



TOXICOLOGICAL REVIEW

OF

THALLIUM and COMPOUNDS

(CAS No. 7440-28-0)

**In Support of Summary Information on the
Integrated Risk Information System (IRIS)**

January 2008

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LIST OF ACRONYMS AND ABBREVIATIONS

AchE	Acetyl cholinesterase
ALA	Aminolevulinic acid
ALT	Alanine aminotransferase
ARDS	Adult respiratory distress syndrome
AST	Aspartate aminotransferase
BMD	Benchmark dose
BUN	Blood urea nitrogen
CASRN	Chemical Abstracts Service Registry Number
ChAT	Choline acetyltransferase
CHO	Chinese hamster ovary
EPA	Environmental Protection Agency
F	Female
GI	Gastrointestinal
GLPs	Good Laboratory Practices
GSH	Glutathione
5-HT	5-Hydroxytryptamine
i.p.	Intraperitoneal
i.v.	Intravenous
IRIS	Integrated Risk Information System
LD₅₀	Median lethal dose
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
M	Male
MAO	Monoamine oxidase
MDA	Malondialdehyde
MED	Minimum effective dose
MEPP	Miniature endplate potential
NA	Nucleus accumbens
NOAEL	No-observed-adverse-effect level
PAD	peripheral arterial disease
RfC	Inhalation reference concentration
RfD	Oral reference dose
s.c.	subcutaneous

SCE	Sister chromatid exchange
SGOT	Serum glutamic oxaloacetic transferase (now termed AST)
SGPT	Serum glutamate pyruvate transaminase (now termed ALT)
SOD	Superoxide dismutase
TI	Thallium
UF	Uncertainty factor

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to thallium and compounds. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of thallium and compounds.

The intent of Section 6, *Major Conclusions in the Characterization of Hazard and Dose Response*, is to present the major conclusions reached in the derivation of the reference dose, reference concentration, and cancer assessment, where applicable, and to characterize the overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing the quality of the data and related uncertainties. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of thallium and compounds. IRIS Summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic and other exposure durations, and a carcinogenicity assessment.

The RfD and RfC, if derived, provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. The RfD (expressed in units of mg/kg-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC (expressed in units of mg/m³) is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). Reference values are generally derived for chronic exposures (up to a lifetime), but may also be derived for acute (≤ 24 hours), short-term (> 24 hours up to 30 days), and subchronic (> 30 days up to 10% of lifetime) exposure durations, all of which are derived based on an assumption of continuous exposure throughout the duration specified. Unless specified otherwise, the RfD and RfC are derived for chronic exposure duration.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposure may be derived. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates may be derived from the application of a low-dose extrapolation procedure. If derived, the oral slope factor is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a unit risk is an upper bound on the estimate of risk per $\mu\text{g}/\text{m}^3$ air breathed.

Development of these hazard identification and dose-response assessments for thallium and compounds has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines and Risk Assessment Forum Technical Panel reports that may have been used in the development of this assessment include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Guidelines for Developmental*

Toxicity Risk Assessment (U.S. EPA, 1991a), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Guidelines for Carcinogen Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA., 2005b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b, 2000a, 2006), *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002).

The literature search strategy employed for this compound was based on the Chemical Abstracts Service Registry Number (CASRN) and at least one common name. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. The relevant literature was reviewed through August 2007.

2. CHEMICAL AND PHYSICAL INFORMATION

Thallium occurs naturally in the earth's crust. Metallic thallium (Tl) is bluish-white or grey, very soft, malleable, and insoluble in water. Thallium is a Group IIIA metal, one whose salts do not hydrolyze at $\text{pH} \geq 7$ to form insoluble hydroxides. According to Mulkey and Oehme (1993), this is a physical property that contributes to thallium's marked toxicity. Thallium exists in monovalent [thallous; thallium (I); Tl^{+1}] and trivalent [thallic; thallium (III); Tl^{+3}] states. Monovalent thallium is favored in the standard potential of $\text{Tl}^{+3}/\text{Tl}^{+1}$ coupling with a redox potential of +1.25V ($\text{Tl}^{+3} + 2\text{e}^-$ goes to Tl^{+1}). According to Pearson (1963), monovalent thallium is a Lewis acid (electron pair receiver) that prefers to interact with inorganic and organic sulfur, carbon, phosphorous and arsenic moieties as the electron pair donor (Lewis base). Monovalent thallium ions also are more stable in aqueous solution, but trivalent thallium (Tl^{+3}) can be stabilized by complexing agents (Sabbioni et al., 1980a). Trivalent thallium forms more stable organic compounds than monovalent thallium.

Monovalent thallium is similar to potassium (K^+) in ionic radius and electrical charge, which contribute to its toxic nature. Many of the thallium salts are soluble in water with the exception of thallium (III) oxide, which is insoluble. Thallium compounds and their chemical and physical properties are listed in Table 1.

According to IPCS (1996), thallium is used only in small amounts by industry, and thus worldwide production of pure thallium is low. Sources for the production of thallium are zinc, lead and sometimes copper or iron smelters and sulfuric acid plants. In 1981 the production of thallium in the United States was discontinued. Thallium is released to the environment through the combustion of fossil fuels (in particular coal-fired power-generating plants), refinement of oil fractions, the smelting of ferrous and non-ferrous ores (including lead, copper and zinc), and by some other industrial processes such as cement production and brick works (IPCS, 1996).

Due to its ability to remove hair, thallium (I) sulfate was used in the past as a depilatory agent. Thallium (I) sulfate was once used in medicine to treat infections such as venereal diseases, ringworm of the scalp, typhus, tuberculosis and malaria. It was also used in the past as a pesticide for various rodents and insects but has been banned for this use in the United States since 1972. Currently thallium is still used in the semiconductor industry and the manufacture of optic lenses. When thallium is alloyed with mercury, it is used on switches and closures, which can operate at subzero temperatures. Thallium compounds are also used to manufacture low-melting glass, low-temperature thermometers, alloys, electronic devices, mercury lamps, fireworks, and imitation gems. Thallium radioisotopes are used in medicine for scintigraphy of certain tissues and the diagnosis of melanoma (Ibrahim et al., 2006; NLM, 1998; IPCS, 1996;

ATSDR, 1992; U.S. EPA, 1991b).

Table 1. Chemical and physical properties of thallium and selected thallium compounds

Name	CASRN	Chemical formula	Molecular weight	Melting point (°C)	Boiling point (°C)	Solubility in water (g/L)
Metallic thallium	7440-28-0	Tl	204.38	303.5	1457	insoluble
Thallium (I) acetate	563-68-8	TlC ₂ H ₃ O ₂	263.43	131	no data	very soluble
Thallium (I) carbonate	6533-73-9	Tl ₂ CO ₃	468.78	273	no data	40.3 (15.5°C)
Thallium (I) chloride	7791-12-0	TlCl	239.84	430	720	very soluble (20°C)
Thallium (I) nitrate	10102-45-1	TlNO ₃	266.39	206	430	95.5 (20°C)
Thallium (III) oxide	1314-32-5	Tl ₂ O ₃	456.76	717	875	insoluble
Thallium (I) selenite	12039-52-0	Tl ₂ SeO ₃	535.72	no data	no data	no data
Thallium (I) sulfate	7446-18-6	Tl ₂ SO ₄	504.82	632	decomposes	48.7 (20°C)

Sources: IPCS (1996); ATSDR (1992).

3. TOXICOKINETICS

3.1. ABSORPTION

Studies in humans and animals indicate that thallium compounds are readily absorbed through various routes of exposure, but few studies provide quantitative measures of absorption. Mulkey and Oehme (1993) reported that water soluble salts are rapidly and completely absorbed from the respiratory tract, gastrointestinal (GI) tract, or skin but did not provide data or cite references to support this conclusion. Thallium ions have been detected in the urine of exposed humans (Ludolph et al., 1986; Davis et al., 1981; Schaller et al., 1980; Cavanagh et al., 1974; Gefel et al., 1970) and animals (Thomas and McKeever, 1993; Waters et al., 1992; Leloux et al., 1987; Talas and Wellhöner, 1983), which implies absorption from environmental sources.

Shaw (1933) determined that 61.6% of an oral dose of thallium (I) sulfate (25 mg Tl/kg) was absorbed by a dog. Lie et al. (1960) determined that thallium was completely absorbed via the GI tract, following oral administration of 767 μg $^{204}\text{Tl}/\text{kg}$, as thallium (I) nitrate. This was based on observations in male Wistar-derived rats where the body burden decreased exponentially and extrapolated to 100% absorption. The same results were obtained when thallium (as thallium nitrate) was administered by other routes of exposure (intravenous [i.v.], 38 $\mu\text{g}/\text{kg}$; intramuscular, 96 $\mu\text{g}/\text{kg}$; subcutaneous, 96 $\mu\text{g}/\text{kg}$; intratracheal, 123 $\mu\text{g}/\text{kg}$; and intraperitoneal [i.p.], 146 $\mu\text{g}/\text{kg}$). Eighty percent of a single dose of 10 nmol of thallium, as thallium (I) sulfate, was absorbed within one hour from tied-off jejunal segments in anesthetized rats (Forth and Rummel, 1975; Leopold et al., 1968).

No information was found regarding the absorption of thallium salts via inhalation. There are a few case reports (Hirata et al., 1998; Ludolph et al., 1986) in which occupational exposure has been associated with toxicity, but it could not be determined if exposure occurred via inhalation or another route (e.g., oral or dermal).

The use of thallium salts in the past as depilatory agents, as a treatment for ringworm of the scalp, and as treatment for night sweats associated with tuberculosis suggests dermal absorption (Léonard and Gerber, 1997; Reed et al., 1963; Lie et al., 1960).

3.2. DISTRIBUTION

Thallium ions are rapidly distributed (as early as 1 hour after exposure) throughout the body in both experimental animals (Careaga-Olivares and Gonzalez-Ramirez, 1995; Galván-Arzate and Rios, 1994; Aoyama, 1989; Rios et al., 1989; Talas and Wellhöner, 1983; Sabbioni et al., 1980a, b; Lameijer and van Zwieten, 1977; Andre et al., 1960; Downs et al., 1960; Lie et al., 1960; Lund, 1956) and humans (Talas et al., 1983; Davis et al., 1981; Cavanagh et al., 1974;

Barclay et al., 1953), regardless of the route of exposure, dose, length of exposure, type of thallium compound, or valence state (Sabbioni et al., 1980a, b; Lameijer and van Zwieten, 1977). The highest thallium concentrations have typically been found in the kidney and the lowest concentrations in the brain, with none being detected in fat tissue. Thallium also has been demonstrated to cross the placenta in humans (Hoffman, 2000) and experimental animals (Gibson and Becker, 1970).

The distribution of thallium in newborn Wistar rats differed from that in adult Wistar rats. Newborns administered an i.p. dose of 16 mg/kg thallium (I) acetate (12.4 mg Tl/kg) had the highest levels of thallium in the testis, heart, and kidneys, in that order, 24 hours after administration (Galván-Arzate and Rios, 1994). Levels in the liver and brain were approximately three- to fourfold lower. In adult rats, the level of thallium in the kidney 24 hours after an i.p. dose of 16 mg/kg thallium (I) sulfate was approximately twofold higher than the level present in the testis (Rios et al., 1989). Galván-Arzate and Rios (1994) also demonstrated age-related differences in the regional distribution of thallium in the brain. Twenty-four hours after i.p. injection of 16 mg/kg thallium (I) acetate, the thallium content among all regions of the brain of newborn rats was homogeneous, whereas the thallium content in the brain of rats 5 to 20 days old showed a region-dependent distribution, with thallium levels in the cortex significantly lower than levels in the hypothalamus.

3.3. METABOLISM

Because thallium is an element, it is not metabolized. It is not known if thallium is transformed from one valence state to another *in vivo*.

3.4. ELIMINATION

Thallium salts are eliminated mainly via urine and feces, but the amount excreted via each route varies depending on the species. Thallium also has been found to be excreted in breast milk, sweat, saliva, and tears (IPCS, 1996). Thallium deposition into hair and nails also is considered an important route of elimination.

In a survey of 776 members of the general population (≥ 40 years of age) that participated in the 1999-2000 National Health and Nutrition Examination Survey (NHANES 1999-2000), the geometric mean level of thallium in the urine was 0.16 $\mu\text{g/L}$, with a maximum of 0.86 $\mu\text{g/L}$ (Navas-Acien et al., 2005).

A study of a human cancer patient orally administered thallium (I) sulfate and radiolabeled thallium (I) nitrate ($^{204}\text{TlNO}_3$) demonstrated that thallium was mainly excreted in the urine; 15.3% of the thallium salts were recovered in the urine over 5.5 days with 0.4% recovered in the feces over 3 days (Barclay et al., 1953). Shaw (1933) demonstrated that 32 and

61.6% of a single oral dose of 25 mg Tl/kg as thallium (I) sulfate administered to a dog was excreted in the urine at 3 and 36 days after dosing, respectively; however, fecal excretion was not measured.

Thallium is excreted to a greater extent in the feces than in the urine of rats and rabbits. Lund (1956) determined that after 26 days, 51.4% of an i.p. dose of 10 mg thallium (I) sulfate/kg in the rat was eliminated via the feces, while 26.4% was excreted in the urine. Talas and Wellhöner (1983) demonstrated that thallium (I) acetate administered to rabbits via i.v. injection (as a radioactive tracer) was excreted mainly in the feces. Both studies found that, although the feces was the major route of excretion in the rat and rabbit, neither species had high levels in the bile, suggesting that excretion via the liver was relatively low. Lund (1956) determined that thallium was mainly excreted in the feces through gastric and intestinal secretions, which is likely associated with potassium excretion. Lund (1956) demonstrated that rabbits excreted thallium through the kidneys by glomerular filtration, but approximately one-half the dose filtered was reabsorbed in the tubuli. In Syrian golden hamsters, thallium (I) sulfate was mainly excreted in the feces after i.p. administration but was excreted at an equal rate in the feces and urine after an oral dose (Aoyama, 1989).

Sabbioni et al. (1980b) determined that thallium (I) sulfate administered at doses of 0.00004 to 2000 µg/rat was persistent in the kidneys for 8 days (192 hours) after dosing with 2.5% of the dose still present at that time. The biological half-life of thallium in rats has been estimated to range from 3–8 days (Lehmann and Favari, 1985; Lie et al., 1960). The biological half-life in humans has been estimated to be approximately 10 days, with values up to 30 days reported (IPCS, 1996).

3.5. PHYSIOLOGICALLY BASED TOXICOKINETIC MODELS

There are no physiologically based toxicokinetic models for soluble thallium salts.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

Studies of thallium toxicity in humans are comprised of clinical reports, case studies, and medical surveys. Because case reports largely involved accidental ingestion, intentional poisoning, or suicide attempts, they do not provide useful information on thallium toxicity associated with chronic exposure. Available epidemiology studies involving long-term exposure to thallium are limited by small study populations and insufficient characterization of long-term exposure. Health effects information was based on self-reporting (via questionnaire) or medical histories/physical examinations of uncertain scope. Table 2 summarizes the individual case reports of human exposure to thallium.

In adults, the average lethal oral dose has been estimated to range from 10 to 15 mg/kg (Schoer, 1984; Gosselin et al., 1984). Without treatment, death typically follows in about 10–12 days, but death as soon as 8–10 hours also has been documented (IPCS, 1996).

4.1.1. Incident/Case Reports

As indicated by case reports, the acute toxicity of thallium is characterized by alopecia (hair loss), severe pain in the extremities, lethargy, ataxia, abdominal pain or vomiting, back pain, abnormal reflexes, neuropathy, muscle weakness, coma, convulsion, other neurological symptoms (i.e., mental abnormalities, tremors, abnormal movements, abnormal vision, and headache), and death (Lu et al., 2007; Tsai et al., 2005; Saha et al., 2004; Sharma et al., 2004; Rusyniak et al., 2002; Atsmon et al., 2000; Hirata et al., 1998; Feldman and Levisohn, 1993; Yokoyama et al., 1990; Heyl and Barlow, 1989; Roby et al., 1984; Limos et al., 1982; Davis et al., 1981; Cavanagh et al., 1974; Gefel et al., 1970; Reed et al., 1963). Symptoms were observable within 14 hours after a high dose (i.e., 5–10 g of thallium (I) nitrate), with death occurring 8 days later (Davis et al., 1981). The lowest known single dose of thallium associated with adverse effects was reported to be 0.31 g of thallium (I) acetate (3.4 mg Tl/kg assuming a 70 kg body weight). This dose caused paresthesia, pain, weakness, vomiting, and alopecia in a 26-year-old male. Approximately 1 month after the onset of symptoms, complete recovery occurred following treatment. In adults, doses ranging from 6 to 40 mg/kg have been reported to be lethal (IPCS, 1996). Table 2 summarizes the individual case reports.

Table 2. Thallium toxicity in humans, following oral exposure

Reference	Sex	Age	Dose	Symptoms	Final outcome
Males — adult					
Gefel et al., 1970	Male	41 years	Unknown but chronic; urine thallium 0.15 mg/100 mL	High blood pressure; lower back pain; vomiting; severe pain in the feet; weakness of the calf muscle; alopecia; slurred speech; atrophic lower limbs; limited vision	Death
Cavanagh et al., 1974	Male	60 years	0.93 g thallium (I) acetate in 2 divided doses	Diarrhea; vomiting; dizziness; back pain; paresthesia of the feet and lower legs; high blood pressure; facial weakness; dysphagia; difficulty breathing	Death within a week of symptoms
Cavanagh et al., 1974	Male	56 years	0.93 g thallium (I) acetate in 3 divided doses	Abdominal pain; diarrhea; vomiting; paresthesia; photophobia, nystagmus, visual impairment; facial weakness; bilateral ptosis	Death within 3 weeks of symptoms
Cavanagh et al., 1974	Male	26 years	0.31 g thallium (I) acetate	Paresthesia in both feet; chest pain; tenderness over the sternum; vomiting, weakness, pain in the knees and ankles that inhibited walking; alopecia	Recovery
Davis et al., 1981	Male	19 years	5–10 g thallium (I) nitrate	Nausea; vomiting; slurred speech; paresthesia of hands and feet; respiratory weakness	Death
Limos et al., 1982	Male	56 years	Unknown	Visual disturbances; alopecia; elevated AST and ALT; high blood glucose and creatine kinase; decreased myelinated fibers; denervated Schwann cell clusters	Bedridden; could not speak
Limos et al., 1982	Male	26 years	Unknown	Visual disturbances; alopecia; elevated AST and ALT; high blood glucose and creatine kinase; decreased myelinated fibers; denervated Schwann cell clusters	Residual tremors of the extremities and muscle weakness of the lower limbs
Roby et al., 1984	Male	45 years	Unknown; urine thallium: 2000 µg/L	Burning pain in feet; inability to walk; alopecia; acute fibrillation	Continued neurological dysfunction

Table 2. Thallium toxicity in humans, following oral exposure

Reference	Sex	Age	Dose	Symptoms	Final outcome
Heyl and Barlow, 1989	Male	“5 young men”	Unknown	Follicular plugging of the skin (nose, cheeks, and nasolabial folds) by keratinous material; crusted eczematous lesions and acneiform eruptions on the face; dry scaling on palms and soles; and alopecia (scalp, eyelashes, lateral eyebrows, arms and legs). Skin biopsies (scalp and cheek): disintegrating hairshafts, gross follicular plugging, and eosinophilic keratohyaline granules in the epidermis; necrotic sebaceous glands; (pustular lesions on the face): folliculitis and necrosis of the follicles; (feet) marked hyperkeratosis and hypergranulosis.	4/5 recovered; 1/5 experienced permanent neurological damage
Yokoyama et al., 1990	Male	31 years	Unknown; urine thallium: 3.5 mg/L	Nausea, vomiting; leg pain; alopecia; abnormal behavior; decreased conduction velocity of fast nerve fibers	Recovery
Hantson et al., 1997	Male	48 years	200 mg thallium (I) sulfate	No overt symptoms within 24 hours; increase in binucleated cells with micronuclei 15 days after exposure	Recovery
Hirata et al., 1998	Male	29 years	Unknown; hair thallium: 20 ng/g (32 months after possible exposure)	Alopecia; abdominal pain; diarrhea; tingling in extremities; neuropathy	Recovery
Atsmon et al., 2000	Male	40 years	Unknown; urine thallium: 7 mg	Weakness of the limbs; vomiting; severe neurological symptoms; alopecia; high blood pressure; increased ALT and AST; Mees lines; decreased visual acuity; bilateral foot-drop	Recovery
Sharma et al., 2004	Male	48 years	Unknown; serum thallium: 870 µg/100 ml urine thallium: 5000 µg/ml	Painful peripheral neuropathy, decreased consciousness	Death

Table 2. Thallium toxicity in humans, following oral exposure

Reference	Sex	Age	Dose	Symptoms	Final outcome
Females — adult					
Roby et al., 1984	Female	51 years	Unknown; serum thallium: 50 µg/100 mL; urine thallium: 5000 µg/L	Numbness and weakness of the legs and hands; alopecia; fluctuating pulse and blood pressure; bradycardia; hypotension	Persistent ventricular ectopy and neurological dysfunction necessitating placement at a nursing home
Roby et al., 1984	Female	61 years	Unknown; serum thallium: 740 µg/100 mL	Burning chest pain; paresthesia; difficulty speaking and swallowing; inability to walk; hypotension; Acute Respiratory Distress Syndrome (ARDS)	Death
Roby et al., 1984	Female	80 years	Unknown; serum thallium: 422 µg/100 mL; urine thallium: 21,600 µg/L	ARDS	Death
Hoffman, 2000	Female	Pregnant; ages not specified	150–1350 mg thallium (I) sulfate	Paresthesia; abdominal pain; muscle weakness; lethargy; alopecia; Mees lines	None specified
Saha et al., 2003	Female	26 years	Unknown; Serum thallium: 12 µg/100 ml	Headache, lethargy, abdominal pain, muscle cramps, joint pain, backache, numbness of fingers, alopecia, erosion of nails	Not specified
Both sexes - adult					
Brockhaus et al., 1981	Both	Not reported	Unknown	Sleep disorders; tiredness; weakness; nervousness; headache; other psychic alterations; neurological and muscular symptoms	Not reported
Schoer, 1984; Gosselin et al., 1984	Both	Adult	10–15 mg/kg thallium	None specified	Death (average lethal dose)
Rusyniak et al., 2002	Both	Various	Unknown; various levels were detected in urine	Myalgia; arthralgia; paresthesia; dysesthesia; joint stiffness; insomnia; alopecia; abdominal pain	Recovery in 7; 5 had ongoing psychiatric problems

Table 2. Thallium toxicity in humans, following oral exposure

Reference	Sex	Age	Dose	Symptoms	Final outcome
Tsai et al., 2006	Both	48-yr old female; 52-year old male	1.5–2 .4 g	Confusion, disorientation, hallucination, anxiety, depression, memory impairment, peripheral neuropathy, erythematous skin rashes, diarrhea, tachycardia, alopecia	Impairment of memory and verbal fluency remained at 6 moths; neuropsychological impairment persisted at 9 months
Lu et al., 2007; Kuo et al., 2005	Both	48 and 52 years	1.5 and 2.3 g/person (estimated); Serum thallium: 950-2056 µg/L Urine thallium: 11,325-14,520 µg/L	Nausea, vomiting; general aching muscle pain; numbness of tongue and mouth within a few hours; severe paresthesia and dysesthesia in hands and feet (one day post-exposure); erythematous rash; diarrhea; urine retention; hyporeflexia; muscle weakness; hypoesthesia; acneiform eruptions; alopecia (1-3 weeks); mees lines (2-3 months). Skin biopsy: parakeratosis; dilated hair follicles filled with keratin and necrotic sebaceous materials; mild epidermal atrophy; vacuolar degeneration of the basal layer. Cutaneous nerve biopsy: axonal degeneration; loss of epidermal nerves indicating involvement of the small sensory nerves (2 months).	At one-year follow-up, persistent paresthesia, dysesthesia, and impairment of small sensory nerve fibers in skin
Children					
Reed et al., 1963	Both	1–11 years	Unknown	Alopecia; lethargy; ataxia; abdominal pain; vomiting; abnormal reflexes; neuropathy; muscle weakness; coma; convulsion	Neurological abnormalities; retardation; psychosis; death
Feldman and Levisohn, 1993	Male	10 years	Unknown; serum thallium: 296 µg/L; urine thallium: 322 µg/24 hours	Alopecia; leg paresthesia; abdominal pain; seizures	Recovery
Hoffman, 2000	Both	Transplacental	Unknown	Premature birth; low birth weight; alopecia	None specified

High blood pressure or fluctuating blood pressure was noted upon hospital admission in several cases (Roby et al., 1984; Cavanagh et al., 1974; Gefel et al., 1970). Elevated serum aspartate aminotransferase (AST, formerly referred to as SGOT) and serum alanine aminotransferase (ALT, formerly referred to as SGPT), high blood glucose, and creatine kinase values also have been noted in case reports of thallium exposure (Atsmon et al., 2000; Limos et al., 1982). The same symptoms were noted across age and sex groupings. Retardation and psychosis were the most common findings in children (1 to 11 years old) after nonlethal thallium exposure. Several cases were so severe that institutionalization was necessary (Reed et al., 1963). Thallium significantly decreased the conduction velocities of faster nerve fibers in a 31-year-old male, who ingested a thallium-containing rodenticide, compared with baseline levels recorded following recovery.

In most case-study reports, thallium was detectable in the urine or tissues. In some cases, thallium could not be definitively associated with the symptoms because other heavy metals were also found in the blood or urine of the subject.

Hantson et al. (1997) evaluated cytogenetic changes in blood from a 48-year-old man who accidentally ingested 200 mg of thallium (I) sulfate intended for rodenticide use. Despite the lack of overt symptoms 24 hours after ingesting the thallium, the man was admitted to the emergency room and Prussian blue treatments were commenced. Blood samples were obtained on days 1 and 15 for cytogenetic analysis. Slight increases in mean sister chromatid exchange (SCE) numbers on days 1 and 15 were not considered related to thallium exposure. A 3.5-fold increase in binucleated cells with micronuclei (35% versus 10% in the historical controls) was noted on day 15. The thallium level was determined to be 14.4 µg/dL in blood at the time of hospital admission, and the concentration in urine was 3804 µg Tl/g creatinine (reference value, <1 µg Tl/g).

Fifty-one case histories of women treated for thallium poisoning following external application of a 3 to 8% thallium (I) acetate ointment were reviewed for signs of possible thallium intoxication (Munch, 1934). Neurological and GI symptoms were observed in 29 cases after an unspecified number of applications with 2 to 24 ounces of the ointment. This was approximately equivalent to a dose of 53 to 636 mg Tl/kg per application using a 5.5% ointment on a 50-kg woman. Alopecia followed several weeks after beginning treatment.

Hoffman (2000) provided case reports and a comprehensive literature review of thallium poisoning that occurred during pregnancy. Exposures were primarily oral, but some of the cases involved dermal exposure. The majority of the doses were unreported, but those doses that were documented ranged from 150 mg to 1350 mg thallium (I) sulfate. Of the 18 cases that met Hoffman's criteria (cases were excluded if maternal or fetal outcomes were not provided), 5 women were exposed during the first trimester and 5 during the second trimester; the remaining

8 were exposed during the third trimester. The ages of the women were not reported. While the mothers developed the classic symptoms of thallium poisoning, including paresthesia, abdominal pain, muscle weakness, lethargy, alopecia, and Mees lines (single transverse white bands occurring on the nails), the only consistent finding in their offspring was a trend toward prematurity and low birth weight. Several of the children had alopecia, particularly those exposed during the third trimester.

4.1.2. Population Surveys

Several published studies have surveyed populations living near a cement plant in Lengerich, a small city in northwest Germany. These populations were studied because of their potential to experience exposure to thallium as a result of its presence as an impurity in pyrite and its release during the roasting of pyrite for use in making some types of cement. Thallium was discharged to outdoor air, deposited in soils, and was taken up by local crops and indigenous plants. People who lived near the plant and consumed large quantities of home-grown foods thus were exposed to thallium through their diets. Prior to 1979, the concentration of thallium in the pyrite was 400 ppm. After 1979, a pyrite with lower levels of thallium (2 ppm) was used.

Brockhaus et al. (1981) conducted an epidemiological study of a group of 1200 people living near the cement plant in Lengerich. Urinary thallium data were also collected from two reference populations without increased thallium intake—one group consisting of 31 persons living in a small (rural) city in northwest Germany, and a second group consisting of 10 persons living in an urban area in Dusseldorf, Germany. The study investigators did not perform specific tests for toxicity but surveyed for the presence of certain symptoms by using questionnaires. Thallium exposure was assessed by measurements in urine and hair. The thallium body burden of the study population was increased over the reference populations, as indicated by a mean urinary thallium level of $5.2 \pm 8.3 \mu\text{g/L}$ (range: <0.1 to $76.5 \mu\text{g/L}$) in the study population compared to the reference population means of $0.4 \pm 0.2 \mu\text{g/L}$ (rural) and 0.3 ± 0.2 (urban) $\mu\text{g/L}$ (range: 0.1 to $1.2 \mu\text{g/L}$). The predominant contributing factor to the thallium burden was consumption of homegrown fruits and vegetables. When the consumption of homegrown foods was restricted, thallium exposure was reduced, as indicated by decreased thallium in the urine. No correlation between dermal or gastrointestinal symptoms and thallium level was observed. There was a negative correlation between thallium and hair loss (13.6% with urine levels $<2 \mu\text{g/L}$, 6.6% with urine levels $2\text{--}20 \mu\text{g/L}$, and 5.9% with urine levels $>20 \mu\text{g/L}$; 10.7% with hair levels $<10 \text{ ng/g}$, 9.6% with hair levels $10\text{--}50 \text{ ng/g}$, and 2.3% with hair levels $>50 \text{ ng/g}$). These data appear to conflict with other reports that indicate hair loss increases with increasing thallium exposure. A positive association was observed among thallium levels in urine or hair and the following self-reported symptoms: sleep disorders, tiredness, weakness, nervousness,

headache, other psychic alterations, and neurological and muscular symptoms (Brockhaus et al., 1981).

Dolgnier et al. (1983) examined the potential developmental effects of thallium in this same German population. Of 300 births registered in Lengerich between January 1, 1978, and August 31, 1979, questionnaires on health status and maternal risk factors were completed by the mothers of 297 infants. One hundred fifty-four urine and 164 hair samples were analyzed for thallium content. All children with suspected congenital malformations or other abnormalities were examined physically and medical histories of mothers were taken. Eleven out of the 297 births were identified as exhibiting congenital malformations or abnormalities (confirmed by a pediatrician) with five major malformations noted. Two of the five major malformations in the study population were determined by the authors to likely be due to hereditary factors.

The observed rate of congenital malformations in the study population (5 out of 297) was compared to the expected rate of 0.8 per 297 births based on annual statistics from the North Rhine-Westphalia region of Germany for 1974–1978. Congenital malformations in the reference population were thought to be underreported because reporting of birth defects is not required on birth certificates in that area of Germany. The study authors noted that other investigations reported an incidence of 2–3% birth defects among live births, a value that is consistent with 1.7% incidence of birth defects in the study population (5/297 for major malformations) and 3.7% (11/297) for all malformations. The study authors concluded that a causal relationship between thallium exposure and congenital malformations in this population was unlikely. However, study deficiencies, including lack of information on exposure to thallium at the time of pregnancy, limit the strength of this study.

Navas-Acien et al. (2005) examined the association between urinary levels of various metals, including thallium, with peripheral arterial disease (PAD) in a cross-sectional analysis of 790 participants in NHANES 1999-2000. Thallium was not associated with PAD in this sample of the U.S. population.

4.1.3. Occupational Exposure

Schaller et al. (1980) examined 128 men (ages 16–62 years) who were exposed to thallium for 1 to 42 years in three cement manufacturing plants in the Franconia region of Germany. Health effects were determined through medical histories and a physical examination for symptoms. Information on the scope of the physical examinations was not provided. Analyses of roasted pyrites and electro-filter dust confirmed the presence of thallium in various production areas in the plants. The median concentration of thallium in the urine in exposed workers was 0.8 µg Tl/g creatinine with a range of <0.3 to 6.3 µg Tl/g creatinine. The range in 20 individuals without known occupational exposure was <0.3 to 1.1 µg Tl/g creatinine (median

concentration not reported). Medical histories and physical examinations did not indicate thallium poisoning. The health status of exposed workers, however, was not compared with an unexposed reference population, and a single measurement of urinary thallium did not provide a measure of past exposures.

Thirty-six cement plant workers (presumably in Germany) were examined for clinical and electrophysiological parameters (Ludolph et al., 1986). Thallium levels were found to be elevated in the blood of 16 workers, urine of 5 workers, and hair of 5 workers. It was not noted if these were all separate cases or if elevations in all three parameters occurred in the same individuals. The study determined that 28–39% of the individuals had some form of peripheral and central motor and sensory impairment. The neurological impairments could not conclusively be attributed to thallium exposure because half the patients suffered from concurrent diseases (including peptic ulcer, diabetes, disorders of joints and connective tissue, and hypertensive vascular disease), which could possibly cause neuromuscular impairment. No controls were employed, and no correlations were made with the levels of thallium in individuals and their disease states.

In another occupational study, Marcus (1985) examined medical records for 86 workers (sex not reported) occupationally exposed to thallium at a magnesium seawater battery factory. Exposure was determined by measuring thallium in urine samples. Marcus also examined the records of 79 unexposed workers matched for age, length of employment, shift pattern, and type of work. Exposed workers did not have an increase in incidence of benign neoplasms or any other clinical diagnoses when compared with unexposed workers. This study is limited by lack of exposure quantitation, the size of the cohort, and unknown length of follow-up.

Although there are many case reports of thallium poisoning in the literature, the doses were largely unknown because ingestion was accidental or occurred through criminal poisoning. Given the severity of reported symptoms, most of the exposures were likely to have been relatively large. The few epidemiology studies that looked at populations surrounding a cement factory that released thallium only attempted to compare thallium exposure with congenital malformations or surveyed symptoms. None of the studies specifically studied cancer as an endpoint. Overall, the available epidemiology literature is considered limited and inconclusive.

4.2. LESS-THAN-LIFETIME AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. Oral Exposure

4.2.1.1. Acute and Subchronic Studies

Rats

In a study performed by Midwest Research Institute (MRI, 1988) for EPA's Office of Solid Waste, male and female Sprague-Dawley rats (45 days old, 20/sex/group) were administered 0 (untreated and vehicle controls), 0.01, 0.05, or 0.25 mg/kg-day of an aqueous solution of thallium (I) sulfate (approximately 0, 0.008, 0.04, or 0.20 mg Tl/kg-day) by gavage for 90 days. The study was conducted in compliance with EPA Good Laboratory Practices (GLPs). MRI (1988) study is an unpublished study; accordingly, it was externally peer reviewed by EPA in November 2006. Body weight, food consumption, hematologic and clinical chemistry parameters, ophthalmic examinations, gross pathologic observations, and organ weights (liver, kidneys, brain, gonads, spleen, heart, and adrenals) were recorded for all animals. Neurotoxicological examinations (3 times/week) were performed on 6 rats/sex/group; these examinations were apparently observational (further details were not provided in the study report). Tissues from 3 rats/sex/group were prepared for neuropathological examination. Complete histopathological examinations (including neuropathological examinations) were conducted for the vehicle control and 0.2 mg Tl/kg-day groups only; for the other three groups, only the livers, lungs, kidneys and gross lesions were examined histopathologically. Neuropathological examinations included the following: dorsal and ventral root fibers of the spinal nerves, dorsal root ganglia, spinal cord at C3-C6 and L1-L4, and six sections of the brain.

There were no statistically significant differences in body weight, food consumption, or absolute and relative organ weights among control groups and groups receiving thallium (I) sulfate. Ophthalmology examinations did not indicate any treatment-related effects. The study authors concluded that the histopathological examination did not reveal any treatment-related effects.

Lacrimation (secretion of tears) and exophthalmos (abnormal protrusion of the eyeball) were observed at higher incidences in the treated rats compared with both controls. The incidence of lacrimation in males (M) and females (F) was as follows: untreated control—1/20 (M), 7/20 (F); vehicle control—6/20 (M), 6/20 (F); 0.008 mg Tl/kg-day—19/20 (M), 20/20 (F); and 0.04 and 0.2 mg Tl/kg-day—20/20 (M and F). The incidence of exophthalmos was as follows: untreated control—1/20 (M), 5/20 (F); vehicle control—5/20 (M), 6/20 (F); 0.008 mg Tl/kg-day—12/20 (M), 19/20 (F); and 0.04 and 0.2 mg Tl/kg-day—20/20 (M and F). Ophthalmic examination and gross and histopathological examination of the eyes, however, revealed no treatment-related abnormalities.

Subtle but statistically significant changes were observed in several blood chemistry parameters that the investigators considered probably treatment related. Specifically, dose-related increases in serum glutamic oxaloacetic transferase (AST), lactate dehydrogenase (LDH), and sodium levels and decreases in blood sugar levels were detected in male and female rats after 30 and 90 days of exposure. Reported values for the selected blood chemistry parameters are summarized in Table 3. Other changes in blood chemistry parameters were less consistent across species, dose groups, and exposure durations.

At 90 days, changes in AST, LDH, sodium, and blood sugar levels in dosed male and female rats were no greater than 31%, 38%, 4%, and 82%, respectively, of the vehicle control group values. The investigators observed that the increases in AST and LDH levels could indicate a possible effect of treatment on cardiac function, that increases in LDH coupled with subtle changes in electrolytes could indicate an effect on renal function, and that, in rare instances, a decrease in blood sugar coupled with an increase in sodium occurs as a defense mechanism for maintaining cellular integrity. The investigators concluded that none of the changes observed in the blood chemistries of males or females during the study were of sufficient magnitude to significantly affect the health status of the animals. Further, histopathological evaluation did not confirm any cellular damage suggested by the clinical chemistry findings.

Clinical observations revealed an increased incidence of alopecia, particularly in female rats at the high dose (see Table 4). Based on a statistical analysis performed by the U.S. EPA¹, the incidence of alopecia (total number of cases in each dose group) was statistically significantly elevated relative to controls in mid-dose males and mid- and high-dose females. Most instances of alopecia in females were attributed to barbering behavior (where fur was present but cropped short). Of the twelve high-dose females with alopecia, five instances were not totally attributed to barbering behavior. Histopathological examination revealed atrophy of the hair follicles in two high-dose female rats. This lesion was not found in other dose groups or the control, but the skin was examined for histopathological changes only in the vehicle control and high-dose groups. The two high-dose females with atrophy of the hair follicles also had alopecia; whether the hair follicle atrophy and alopecia occurred at the same location on the rats could not be determined from the study report. The authors noted that the cases of alopecia that were not totally attributed to barbering behavior occurred in various anatomical locations, thereby lessening the likelihood of chemical effect. They further observed that based on microscopic evaluation, the alopecia was attributable to the cyclic pattern of hair growth in

¹ A statistical analysis of the incidence of alopecia (based on the total number of cases of alopecia in each dose group) was performed by the U.S. EPA using Fisher's exact test. Incidence in the treated groups was compared to incidence in the untreated control, vehicle control, and pooled control.

rodents. Consequently, the authors did not consider these findings to be biologically significant and identified the highest dose, 0.25 mg/kg-day thallium (I) sulfate (0.20 mg Tl/kg-day), as the no-observed-adverse-effect level (NOAEL). Upon further analysis of the MRI (1988) findings as part of this health assessment, a different determination was reached regarding the NOAEL and LOAEL; see the discussion in Section 5.1.1.

Table 3. Selected blood chemistry values

Blood chemistry parameter	Study day	Untreated control	Vehicle control	0.008 mg/kg-day	0.04 mg/kg-day	0.2 mg/kg-day
Males^a						
AST (I.U.)	30	91 ± 26.5	108 ± 18.6	128 ± 24.5 ^b	134 ± 29.0 ^{b,c}	152 ± 20.1 ^{b,c}
	90	77 ± 19.7	87 ± 17.8	99 ± 20.4	113 ± 27.0 ^{b,c}	114 ± 31.1 ^{b,c}
LDH (I.U.)	30	795 ± 322	1206 ± 424 ^b	1333 ± 340 ^b	1396 ± 407 ^b	1802 ± 341 ^{b,c}
	90	587 ± 305	856 ± 385	1003 ± 363 ^b	1071 ± 507 ^b	1119 ± 477 ^b
Na (meq/L)	30	148 ± 1.3	149 ± 2.4	152 ± 4.0 ^b	154 ± 2.5 ^{b,c}	153 ± 2.1 ^{b,c}
	90	144 ± 1.6	147 ± 2.0 ^b	147 ± 1.9 ^b	149 ± 2.0 ^{b,c}	151 ± 2.2 ^{b,c}
Blood sugar (mg/100 mL)	30	100 ± 22.1	97 ± 18.1	93 ± 10.0	90 ± 18.3	62 ± 14.8 ^{b,c}
	90	158 ± 15.6	138 ± 16.8 ^b	131 ± 17.6 ^b	121 ± 15.7 ^b	113 ± 22.4 ^{b,c}
Females^a						
AST (I.U.)	30	95 ± 22.8	115 ± 30.3	127 ± 27.8 ^b	149 ± 26.8 ^{b,c}	154 ± 18.2 ^{b,c}
	90	77 ± 19.2	90 ± 19.1	93 ± 33.1	111 ± 30.7 ^b	112 ± 31.0 ^b
LDH (I.U.)	30	1047 ± 335	1277 ± 495	1402 ± 501	1763 ± 370 ^{b,c}	1764 ± 361 ^{b,c}
	90	745 ± 320	881 ± 273	823 ± 354	1044 ± 436	1219 ± 338 ^b
Na (meq/L)	30	148 ± 1.7	150 ± 1.9	153 ± 4.1 ^{b,c}	154 ± 2.8 ^{b,c}	155 ± 2.5 ^{b,c}
	90	146 ± 1.8	146 ± 1.0	148 ± 1.8 ^{b,c}	150 ± 2.0 ^{b,c}	152 ± 1.0 ^{b,c}
Blood sugar (mg/100 mL)	30	103 ± 23.9	80 ± 13.3 ^b	80 ± 9.0 ^b	67 ± 20.0 ^b	50 ± 11.8 ^{b,c}
	90	110 ± 28.7	89 ± 15.9	103 ± 19.9	88 ± 20.4	70 ± 18.0 ^b

^aMean ± SD of 7 to 10 rats.

^bSignificantly different ($p < 0.05$) from the untreated control group.

^cSignificantly different ($p < 0.05$) from the vehicle control group.

Source: MRI (1988).

Table 4. Incidence of alopecia in rats

Dose (mg TI/kg-day)	Males		Females	
	Alopecia ^{a, b}	Hair follicle atrophy ^c	Alopecia ^{a, b}	Hair follicle atrophy ^c
0 (untreated control)	2/20	-- ^d	4/20	-- ^d
0 (vehicle control)	1/20	0/20	1/20	0/20
0.008	4/20	-- ^d	4/20	-- ^d
0.04	9/20 ^e	-- ^d	9/20 ^f	-- ^d
0.2	4/20	0/20	12/20 ^e	2/20

^a Number of animals with alopecia at least once during the 90-day study based on clinical observations.

^b Of the animals with alopecia, the following are the numbers of cases in each dose group that the study authors stated were “not totally attributed to barbering behavior”:

Males: untreated control – 1; vehicle control – 0; 0.008 mg/kg-d – 2; 0.04 mg/kg-d – 4; 0.2 mg/kg-d – 1.

Females: untreated control – 0; vehicle control – 0; 0.008 mg/kg-d – 1; 0.04 mg/kg-d – 3; 0.2 mg/kg-d – 5.

^c Based on histopathological observation.

^d Skin was not examined for histopathological lesions.

^e Incidence of alopecia (total number of cases) was statistically significantly elevated ($p < 0.05$) relative to incidence in vehicle control, incidence in untreated control, and pooled incidence of vehicle and untreated control, based on Fisher’s exact test performed by the U.S. EPA.

^f Incidence of alopecia (total number of cases) was statistically significantly elevated ($p < 0.05$) relative to incidence in vehicle control and pooled incidence of vehicle and untreated control, based on Fisher’s exact test performed by the U.S. EPA.

Source: MRI (1988)

Manzo et al. (1983) administered drinking water containing thallium (I) sulfate at a concentration of 10 mg TI/L (approximately equivalent to a dose of 1.4 mg TI/kg-day based on reported thallium intakes and an assumption that the rats weighed 200 g) to 80 female Sprague-Dawley rats for 36 weeks. Mortality was 15 and 21% after 40 and 240 days of treatment, respectively. After 4+ weeks (32 days) of treatment, hair loss appeared and involved about 20% of the animals thereafter. Functional and histopathological changes were observed in the peripheral nerves, including changes in motor and sensory action potentials and histopathological changes in the sciatic myelin sheath and axonal destruction characterized by Wallerian degeneration (degeneration of the axon and its myelin sheath distal to a site of injury), mitochondrial degeneration, neurofilamentous clustering, and elevated lysosomal activity.

Ten adult male albino rats were administered 0.8 mg/kg (1/20th of the LD₅₀) of thallium (I) sulfate orally (presumably via gavage) for 3 months (El-Garawany et al., 1990). Blood samples were obtained initially and at monthly intervals. At all three monthly intervals, the treated group had statistically significantly ($p < 0.001$) increased levels of blood urea, serum

creatinine, serum bilirubin, and serum ALT. The largest increase (<90%) in these parameters occurred in the first month with smaller increases (>15%) occurring for each additional month.

Mourelle et al. (1988) examined the effects of silymarin, an antioxidant, on various biochemical indicators of liver damage in male Wistar rats (200-250 g) induced by oral (gavage) administration of thallium (I) sulfate (10 mg/kg) dissolved in water. The controls were given vehicle only. Ten rats per group were sacrificed at 0, 24, 48, 72, and 96 hours and 5, 10, and 20 days after treatment. Without silymarin administration, thallium administration produced a statistically significant ($p<0.05$) decrease in the content of glycogen and reduced glutathione and a statistically significant ($p<0.05$) increase in malondialdehyde (MDA) production and triglycerides in the liver 48 hours after treatment. (Malondialdehyde production and reduced glutathione content in the liver served as indicators of lipid peroxidation.) Levels of serum alkaline phosphatase were increased and liver cell membrane alkaline phosphatase activity was decreased after 24 hours and remained unchanged for 5 days. Further, Na^+/K^+ -ATPase activity in the liver cell membranes was rapidly reduced within 24 hours of thallium treatment; the decrease persisted through day 5 and began to rebound by day 10 with values similar to the control by day 20. Serum and liver cell membrane gamma-glutamyl transpeptidase and serum ALT were significantly ($p<0.001$) elevated by 24 hours and remained elevated through day 5. Administration of silymarin (100 mg/kg i.p.) completely prevented these biochemical changes. The authors suggested that silymarin acted by stabilizing membranes via some antioxidant property. During the 20 days, none of the rats treated with thallium alone died, but the rats exhibited signs of toxicity that included hypomotility and piloerection.

Downs et al. (1960) fed groups of Wistar-derived albino rats (5/sex/dose) diets containing nominal concentrations of 0, 5, 15, or 50 mg thallium (I) acetate/kg (or ppm) in the diet (corresponding to approximately 0, 0.4, 1.2, and 3.9 mg Tl/kg body weight-day for 100 g rats, assuming food consumption of 10 g/day). Animals were allowed ad libitum access to these diets for 15 weeks. At the 50 ppm dose level, mortality was 100% by week 5 in males and by week 13 in females. By week 15, 4/10 control animals died (2/sex), making interpretation of survival in the remaining dose groups difficult (15 ppm, 3/5 males and 1/5 females died; 5 ppm, 2/6 males and 0/4 females died). An additional treatment group (30 ppm) and control group (corresponding to 0 and 2.4 mg Tl/kg body weight-day) were added 6 weeks after the study had been initiated and were maintained on the diet for 9 weeks. At the end of the 9 weeks, 2/5 male and 1/5 female controls were dead and 4/5 males and 3/5 females at 30 ppm were dead. At termination, the only gross finding was alopecia in the 15 and 30 ppm groups. The alopecia was noted beginning 2 weeks after commencement of the diet, with the rats nearly free of hair at termination. The authors reported a slight increase in kidney weight (doses not specified, data not shown). The authors also reported that histopathologic evaluations did not indicate

treatment-related pathology, but they did not prepare skin sections. The study findings for alopecia suggest a NOAEL and lowest-observed-adverse-effect level (LOAEL) of 0.4 mg Tl/kg-day and 1.2 mg Tl/kg-day, respectively, for this endpoint. Because mortality occurred in rats in both the control and treated groups, it is not possible to determine whether the deaths in low-dose (5 ppm) male rats were related to thallium exposure. Therefore, a NOAEL and LOAEL cannot be reliably established for this study.

Downs et al. (1960) also examined the effects of thallium (III) oxide on weanling Wistar-derived albino rats (5 rats/sex/treatment). Rats received 0, 20, 35, 50, 100, or 500 mg thallium (III) oxide/kg (or ppm) in the diet for 15 weeks. This was equivalent to doses of 0, 1.8, 3.1, 4.5, 9.0, or 44.8 mg Tl/kg body weight-day, respectively. All rats (males and females) treated with 50 ppm and greater in the diet died before 8 weeks. The mortality rates in the remaining groups at 15 weeks were as follows: 1/5 control males, 0/5 males treated with 20 ppm, and 4/5 males treated with 35 ppm; 0/5 control females, 2/5 females treated with 20 ppm, and 2/5 females treated with 35 ppm. Thallium (III) oxide caused a dose-related decrease in body weight at 15 weeks. Body weight reductions relative to the control were 50 and 180 grams in males treated with 20 and 35 ppm dietary doses, respectively, and 50 grams in females treated with 35 ppm in the diet. Males treated with either 20 or 35 ppm in the diet had marked hair loss beginning around 4 weeks, with near complete hair loss after 6 weeks; females were less affected.

There was a statistically significant ($p \leq 0.05$) increase in absolute kidney weights in males and females treated with 20 ppm and females treated with 35 ppm and a dose-response trend in kidney to body weight ratio. Histopathological examination did not reveal any alterations in the kidney related to thallium treatment. Histopathological evaluation of the skin revealed a decrease in the number of hair follicles and hair shafts, atrophy of the remaining follicles, decrease in the size of the sebaceous glands, and hyperkeratinized epidermis. However, the incidence by dose was not presented. The lowest level tested, 1.8 mg Tl/kg-day (20 ppm thallium (III) oxide in the diet), is considered to be a LOAEL based upon findings of alopecia and significant elevations in kidney weights for male and female rats. A NOAEL was not identified for this study.

Leloux et al. (1987) investigated the acute toxicity of oral exposure to thallium (I) nitrate in the adult Wistar rat. In the first experiment, a single dose of 20 mg/kg thallium (I) nitrate was administered via gavage to male and female rats (3 per sex); all males and females were found dead within 40 and 54 hours post-dosing, respectively. Increases in absolute kidney (36%, females; 61%, males) and adrenal (47%, females; 100%, males) weights were observed following the single exposure. The second experiment involved administering four daily gavage doses of 1 mg/kg-day thallium (I) nitrate to 20 animals of each sex. Male rats treated with 4 doses began to lose their hair 96 hours after the first exposure. All treated animals had diarrhea.

Two of the 20 males and 2/20 females died after the fourth gavage dose. Two more females died within 126 hours, and 11 females and 15 males died within 168 hours. Three rats of each sex were sacrificed at 126 hours post-dosing for gross pathological examination and organ weight changes. The remaining two females were sacrificed at 192 hours post-dosing. Treated animals weighed less than the untreated controls. The tissues did not demonstrate any macroscopic degenerative changes, but there was an increase in the absolute weights of the kidneys (33%, females; 48%, males) and eyes (54%, females; 34%, males). Histopathology was not performed.

Dogs

Reports of thallium toxicity in dogs are limited to a few cases in the literature of accidental exposure. A nine-month-old Doberman pinscher accidentally consumed mole bait containing 1% thallium (Waters et al., 1992). Two days later the dog was lethargic, vomited blood, and had bloody feces. The dog had moderate hypoproteinemia and a slight prolonged activated clotting time. The dog's condition was improved by the third day following supportive care, including treatment with activated charcoal.

Thomas and McKeever (1993) reported a case of a one-year-old neutered male miniature schnauzer that had ingested an unknown amount of bread soaked in thallium (the level in one piece of bread was 1.6 ppm). Beginning symptoms were lethargy followed two weeks later by severe, rapidly progressing alopecia. No abnormalities were found in a CBC count, serum chemistry profile, urinalysis, or abdominal radiographs. Diphenylthiocarbazon treatments (40 mg/kg three times daily) were started upon establishing thallium toxicity. On the second day of veterinary treatment, the dog showed signs of respiratory distress and was euthanized due to its poor condition. An autopsy revealed severely congested and edematous lungs, congestion of the liver and kidneys, and areas of congestion and hemorrhage in the pancreas. Histological evaluations demonstrated abnormalities in the lungs, kidneys, liver, and pancreas. Thallium was detected in the liver (11 ppm), kidneys (12 ppm), and spleen (7 ppm).

Histopathology of the skin from 13 cases of thallium poisoning in dogs revealed dyskeratotic and necrolytic changes in the skin and hair follicles (Schwartzman and Kirschbaum, 1961). The most prominent features were massive parakeratosis, spongiform abscess formation and induction of telogen follicles.

4.2.1.2. Chronic Studies and Cancer Bioassays

There are no chronic animal studies or cancer bioassays for thallium reported in the literature.

4.2.2. Inhalation Exposure

No studies were identified that examined the effects of inhaled thallium in animal models.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES

Reproductive Toxicity

Effects of thallium on male reproduction have been investigated in rats (Formigli et al., 1986; Gregotti et al., 1985; Zasukhina et al., 1983) and mice (Wei, 1987). These studies suggest that thallium exposure can produce effects on the testes and sperm. None of the available reproductive toxicity studies, however, used standard protocols for evaluating reproductive endpoints. No studies of the potential reproductive toxicity of thallium in female experimental animals were identified.

Male Wistar rats (10/group) were administered drinking water containing 10 ppm thallium (I) sulfate (approximately 0.7 mg Tl/kg-day based on reported daily thallium consumption [270 µg Tl/rat] and initial body weights [350–380 g]) (Formigli et al., 1986). The compound was administered for 30 and 60 days. Although the study authors stated that the controls were pair-fed, they also stated that food was available ad libitum, and that thallium did not affect food consumption. No abnormalities were observed after 30 days of treatment. However, after 60 days of treatment, the following testicular effects were observed: disarrangement of the tubular epithelium, cytoplasmic vacuolation and distention of smooth endoplasmic reticulum of the Sertoli cells, reduced testicular β -glucuronidase activities (an enzyme primarily located in the Sertoli cell and spermatogonia), high concentrations of thallium in the testes, and reduced sperm motility. Plasma testosterone levels were within normal limits. β -Glucuronidase activity was also affected after 60 days of treatment and ultrastructural changes were observed in the Sertoli cells. From these results, a LOAEL of 0.7 mg Tl/kg-day (10 mg/L) was identified.

Gregotti et al. (1985) also reported β -glucuronidase activity and ultrastructural changes in the Sertoli cells after 60 days of treatment. Gregotti et al. (1992) further examined this effect in vitro and demonstrated that thallium (even at the lowest Tl concentration) causes a dose- and time-dependent detachment of germ cells from Sertoli cells when testicular cells were treated with thallium concentrations corresponding to 1.4, 7, and 35 µg Tl/g testis, estimated from protein content of cultures.

Zasukhina et al. (1983) performed a dominant lethal test with male rats that were given daily oral doses of thallium (I) carbonate (0.005, 0.05, and 0.5 µg/kg-day) for 8 months and subsequently mated with untreated females. The authors reported a treatment-related enhancement of embryonic mortality. Confidence in the reported findings is low, however,

because of inadequate reporting (e.g., the paper did not report the number of male rats exposed or the rat strain), the relatively small number of pregnant females (16–18 per group), and lack of statistical analysis. Further, the low and mid doses used in this study are smaller than the average daily intake for the general population (7 µg/day for a 70-kg adult or 0.1 µg/kg-day) (ATSDR, 1992).

Wei (1987) administered 0, 0.001, 0.01, 0.1, 1.0, or 10.0 mg/L thallium (I) carbonate in drinking water for 6 months to groups of male Kunming mice (10-20/group) weighing 15–20 grams at study initiation. At the end of the exposure period, half of the males were sacrificed for epididymal sperm examination, and half were mated with untreated females. Water intake, body weights, behavior, and animal health were reportedly assessed; however, this information was not provided in the study report, and numbers of animals examined for sperm and reproductive endpoints were ambiguously reported. The author reported that sperm motility (rapid speed, sperm immobility) was affected at the lowest dose (0.001 mg/L) tested. Effects were shown to increase with increasing dose, thus indicating a dose-response relationship. At 0.01 mg/L and higher, the number of dead sperm significantly increased and the number of dead fetuses in females mated to treated male mice increased. Sperm counts were significantly reduced and the percent of deformed sperm increased at doses of 0.1 mg/L and higher. The author indicated that there was an adverse effect on sperm quality (motility) at low doses, but as the dose increased there was an accompanying decrease in sperm count in addition to the motility change. However, the reproductive index (number of pregnant female mice/number of mating female mice) and the number of implantations were not statistically different between treated and control animals. Reported results suggest that the lowest dose tested (0.001 mg/L thallium (I) carbonate) was a LOAEL. Failure to report age of the mice at study initiation, water consumption, and terminal body weight data, and use of a nonstandard strain of mice limit the utility of this study for dose-response assessment.

Table 5 summarizes thallium toxicity in animals following oral exposure.

Table 5. Thallium toxicity in animals, following oral exposure

Reference	Species	Age	Sex	Route	Dose and duration	NOAEL	LOAEL	Effect
Acute studies								
Leloux et al., 1987	Rat n=3/sex	Adult	Both	Oral (gavage)	20 mg/kg thallium (I) nitrate; single dose	NI ^a	15 mg/kg Tl	Difficulty breathing; rough coat; increased absolute kidney, adrenal weights; death
Leloux et al., 1987	Rat n=10/sex/ group	Adult	Both	Oral (gavage)	0, 1 mg/kg thallium (I) nitrate; once daily for 4 days	NI	0.77 mg/kg Tl	Alopecia; diarrhea; increased absolute kidney, eye weights; death
Mourelle et al., 1988	Rat n = 10/group	NS ^b	Male	Oral (gavage)	0, 10 mg/kg thallium (I) sulfate; single dose. Sacrificed at 24 hours to 2 days after dosing	NI	8.1 mg/kg Tl	Liver changes: increased triglycerides and lipid peroxidation; decreased glutathione and glycogen; increased alkaline phosphatase in serum and liver cell membranes
Subchronic studies								
Downs et al., 1960	Rat/ n=5/sex/ group	NS	Both	Oral (feed)	0, 5, 15, or 50 ppm thallium (I) acetate (corresponding to 0, 0.4, 1.2, or 3.9 mg Tl/kg-day); 15 weeks 0 or 30 ppm (corresponding to 0 or 2.4 mg Tl/kg-day); 9 weeks	0.4 mg Tl/kg-day*	1.2 mg Tl/kg-day*	Alopecia; increased kidney weight; mortality in treated and control groups *The NOAEL and LOAEL are for alopecia. Because of reported mortality in the control and treated groups, a study NOAEL and LOAEL cannot be reliably determined.

Table 5. Thallium toxicity in animals, following oral exposure

Reference	Species	Age	Sex	Route	Dose and duration	NOAEL	LOAEL	Effect
Downs et al., 1960	Rat n=5/sex/ group	Weanling	Both	Oral (feed)	0, 20, 35, 50, 100, and 500 ppm thallium (III) oxide (corresponding to 0, 1.8, 3.1, 4.5, 9.0, and 44.8 mg Tl/kg-day); 15 weeks	NI	1.8 mg Tl/kg- day (20 ppm)	Reduced body weight; alopecia; increased mortality; increased absolute and relative kidney weights
El-Garawany et al., 1990	Rat n=10	NS	Male	Oral ^c	0.8 mg/kg thallium (I) sulfate; 90 days	NI	0.65 mg Tl/kg-day	Increased blood urea; serum creatinine; serum bilirubin; serum ALT
Manzo et al., 1983	Rat n=80	NS	Female	Oral (DW ^d)	10 mg Tl/L as thallium (I) sulfate; 36 weeks	NI	1.4 mg Tl/kg- day	Nerve histopathology; alopecia; mortality
MRI, 1988	Rat n=20/sex/ group	45 days	Both	Oral (gavage)	0, 0.01, 0.05, or 0.25 mg thallium (I) sulfate/kg; 90 days	0.04 mg Tl/kg-day ^e	0.20 mg Tl/kg-day ^e	Increased incidence of alopecia, lacrimation, and exophthalmos; statistically significant increases in AST, LDH, and sodium levels; decreased blood sugar levels. The study authors identified 0.2 mg Tl/kg- day as the NOAEL.
Reproductive toxicity								
Formigli et al., 1986	Rat n=10/ group	Adult	Male	Oral (DW)	0, 10 ppm thallium (I) sulfate; 30 or 60 days	NI	0.7 mg Tl/kg- day	Testicular effects: tubular epithelium disarrangement; cytoplasmic vacuolation; reduced sperm motility; distention of smooth endoplasmic reticulum of Sertoli cells; reduced β -glucuronidase activity

Table 5. Thallium toxicity in animals, following oral exposure

Reference	Species	Age	Sex	Route	Dose and duration	NOAEL	LOAEL	Effect
Wei, 1987	Mouse	NS	Male	Oral (DW)	0, 0.001, 0.01, 0.1, 1.0, and 10 mg/L thallium (I) carbonate; 6 months		Cannot be calculated due to non-reporting of water intake, body weights within dose groups	Decreased sperm motility and counts; increase in deformed sperm; decrease in live fetuses
Rossi et al., 1988	Rats	Fetus – 60 days	Both	Mother's DW then dam's (DW)	0, 1 mg/dL of thallium (I) sulfate Day 1 of gestation to weaning then thru 60 days	NI	NI	Prenatal and postnatal exposure caused a delay in the development of the pilus apparatus by 50 days; reduction of the α - and β -adrenergic and muscarinic vasomotor reactivity noted.

^aNI = not identified.

^bNS = not specified.

^cPresumably via gavage.

^dDW = drinking water.

^eSee discussion of the NOAEL and LOAEL determination in Section 5.1.1.

Developmental Toxicity

Developmental toxicity studies in the rat (Rossi et al., 1988; Gibson and Becker, 1970; Barroso-Moguel et al., 1992) and chicken embryo (Hall 1972, 1985; Karnofsky et al., 1950) provide evidence that thallium exposure during development can produce abnormalities (including effects on the developing vascular autonomic nervous system and bones) and reduced fetal body weight. Of the studies in rats, only one involved oral drinking water exposure to thallium (Rossi et al., 1988); in other developmental rat studies, dams were exposed by i.p. injection.

A group of NOS albino male and female rats was administered 1 mg/dL of thallium (I) sulfate from day 1 of gestation to weaning (22 days after birth) via the dam's drinking water, then through their own drinking water until 60 days of age (Rossi et al., 1988). These rats were considered prenatally exposed. Another set of NOS albino male and female rats were exposed to 1 mg/dL of thallium (I) sulfate via the dam's drinking water from birth until weaning (22 days after birth) then through their own drinking water until 60 days of age. These rats were considered postnatally exposed. Both situations (pre- and postnatal exposure) caused a delay in the development of the pilus apparatus by 50 days. A reduction of the α - and β -adrenergic and muscarinic vasomotor reactivity also was noted. Authors noted that this reduction may be due to one of the following mechanisms: probable reduction in the number and/or sensitivity of both α - and β -adrenergic and muscarinic receptors or a change of cell membrane in relation to a possible modification of potassium cell concentration.

Gibson and Becker (1970) administered thallium (I) sulfate (i.p.) to pregnant Simonsen Sprague-Dawley rats during early (2.5 mg/kg on days 8, 9, and 10) or late (2.5 or 10 mg/kg on days 12, 13, and 14) gestation. Fetuses were examined for abnormalities. All three thallium treatments caused a statistically significant ($p < 0.05$) reduction in fetal body weight. Thallium treatment (2.5 mg/kg) during early gestation caused a slight (not statistically significant) increase in the incidence of hydronephrosis (29% in treated versus 16% in control) and missing or non-ossified vertebral bodies (36% in treated versus 17% in controls). The 2.5 mg/kg thallium (I) sulfate treatment administered during late gestation caused a statistically significant ($p < 0.05$) increase in the incidence of hydronephrosis (47% in treated versus 16% in control) and missing or non-ossified vertebral bodies (60% in treated versus 17% in controls). Increasing the dose to 10 mg/kg thallium (I) sulfate during late gestation did not increase the incidence of developmental abnormalities. In fact, 10 mg/kg thallium (I) sulfate administered during late gestation had no effect on the incidence of hydronephrosis and was comparable to the 2.5 mg/kg dose administered during late gestation in the induction of missing or non-ossified vertebral bodies (i.e., 60% in treated versus 17% in controls). Maternal toxicity (diarrhea, lethargy, irritability, poor hair luster, and hair loss) was noted.

Barroso-Moguel et al. (1992) administered a single i.p. injection of 32 mg/kg aqueous thallium (I) acetate to 20 newborn (24-hour-old) Wistar rats. Results were compared with those of five vehicle controls. Rats (four treated and one control per time point) were sacrificed at 24, 48, and 72 hours and at 7 and 50 days. Cartilaginous and osseous tissue alterations were noted. Diarrhea was observed through 72 hours post-injection. Two rats surviving to 50 days postinjection had persisting alopecia (one irreversible and one with discrete recovery). Although skeletal images of 72-hour-old animals did not show any differences when compared with the control, microscopic images of the distal third of the tibia showed disorganization and edema of the fibroblasts of the fibrous layer. By day 7, delays in ossification in the right forelimb were noted. Microscopic examination demonstrated a majority of pycnotic chondrocytes and the lack of bone trabeculae calcification. Profound skeletal alterations were noticeable 50 days after injection. Many of the cartilaginous cells were altered or dead, leading to a decrease of the growth cartilage, scanty bone trabeculae with few osteoblasts. The bone marrow also had few myeloblasts and megakaryocytes.

Hall (1972) incubated chick embryos in a forced-draft Humidaire incubator and injected 0.6 mg thallium (I) sulfate/0.5 mL saline into each embryo via the chorioallantoic membrane at 7 days of incubation. This dose caused a minimal lethal effect with survival varying from 94 to 100%. Treated embryos were smaller than controls from 10 days of incubation onward and by 18 days were 26% smaller than controls. Treated embryos failed to commence ossification or had not progressed to similar developmental stages observed in the control. The long bones of treated embryos were smaller (the tibia to a greater degree than the femur), contained less organic material, and contained more water (as a percent of dry weight) than the untreated control embryos. An abnormal distribution of the acid mucopolysaccharides and necrotic areas in maturing hypertrophic chondrocytes were detected histologically. In addition, biochemical assays verified the reduced acid mucopolysaccharide activity. Hall (1985) further demonstrated that the critical period of susceptibility ended at 8 days of incubation. Tibial growth was inhibited by thallium sulfate in 8-day-old embryos but not in 9-day-old embryos.

Achondroplasia (a birth defect characterized by imperfect bone formation) also was induced in embryonic chicks via in vitro cultures (Hall, 1985) with injection into the chorioallantoic membrane (Hall, 1972) or injection into the yolk sac (Karnofsky et al., 1950). Karnofsky et al. (1950) determined that thallium (I) sulfate was lethal to two-day embryos at a dose lower than would be necessary to induce achondroplasia. Treatment of 4-day-old chick embryos with 0.2, 0.5, 1.0, or 2.0 mg/egg induced 0, 45, 92, and 100% incidence of achondroplasia, respectively. Although the data were not presented, the study authors reported that thallium (I) nitrate produced achondroplasia at similar doses.

4.4. OTHER ENDPOINT-SPECIFIC STUDIES

A number of investigators have specifically examined the effect of thallium compounds administered to experimental animals by injection (subcutaneous, i.p., or i.v.), and reported effects on the liver, kidneys, heart, and nervous system.

4.4.1. Liver and Kidney Toxicity

Liver and kidney were among the organs affected when male and female Sprague-Dawley rats were given subcutaneous injection of thallium (I) acetate as acute (single dose of 20-50 mg/kg), subacute (2-3 weekly injections of 10-15 mg/kg), or chronic (10-20 mg/kg, followed by weekly injections of 5 mg/kg or occasionally 2.5 mg/kg for up to 26 weeks) exposures. Toxicity was observed in all treatment groups (Herman and Bensch, 1967). Animals dosed acutely displayed the symptoms earlier than those on subacute or chronic dosing schedules. Animals were sacrificed when signs of toxicity became apparent.

Acutely exposed animals had the following changes observed via light microscopy: eosinophilic granular casts in 50-75% of the renal proximal and distal tubules, mild to moderate enteritis, moderate to severe colitis, and dense infiltration of polymorphonuclear leukocytes and lymphocytes that extended through all layers of the wall of the large intestine. Electron microscopy revealed severe degenerative changes in the mitochondria of the renal tubules and hepatocytes. The subacutely treated rats had eosinophilic granular casts were in one-third of the proximal and distal tubules. Electron microscopy revealed moderately prominent mitochondrial granules in the kidney, dense bodies in the cytoplasm of the cells in the loops of Henle, and distal convoluted tubules. Mitochondrial granules of hepatocytes were slightly enlarged and lacked electron-lucent cores.

In the chronically exposed rats, electron microscopy revealed increased size of mitochondrial granules in the proximal convoluted and an increase in cup-shaped mitochondria in the distal convoluted tubules. Hepatocytes had increased numbers of large complex residual bodies and lipid droplets, and the mitochondria were swollen with enlargement of mitochondrial granules.

Yoshida et al. (1997) administered a single i.p. injection of thallium (I) sulfate (25 mg/kg) to ICR mice (30–35 g). As was observed in Mourelle et al. (1988) after a single oral dose of thallium (I) sulfate (10 mg/kg) to Wistar rats, liver Na^+/K^+ -ATPase was statistically significantly decreased by 12 hours. However, the rebound occurred by 24 hours instead of the 5 days observed in the Mourelle et al. (1988) study. While the Na^+/K^+ -ATPase activity was decreased, the ATP levels were increased and returned to control values by 12 hours post-dosing. The effects were slightly different in the kidney. At 6 hours Na^+/K^+ -ATPase activity was statistically significantly decreased but had rebounded by 12 hours. The ATP levels were

significantly ($p < 0.01$) increased through 12 hours, then decreased to levels significantly ($p < 0.01$) lower than controls by 24 hours; ATP levels did not rebound until 240 hours after thallium administration.

Male albino rats (210–260 g) receiving a single i.p. injection of 30, 60, or 120 mg/kg thallium (I) sulfate had statistically significant ($p < 0.05$) increased levels of AST and ALT above controls (0.5 mL of 0.9% saline) 16 hours after treatment, regardless of dose (Leung and Ooi, 2000). There was a dose-dependent increase in ALT and AST between 30 and 60 mg/kg, but the levels did not increase between 60 and 120 mg/kg. Some 30-mg/kg animals exhibited weakness, sluggishness, loss of hair, ptosis of the eyelids, diarrhea, and respiratory difficulty; they were sacrificed 4 days post-dosing. The ALT and AST levels in these animals were still elevated over the controls by a factor of 2–2.5. Serum creatinine levels also were elevated by approximately 2.5 times over the control (0.5 mg/dL control versus 1.33 mg/dL treated). Histological evaluation confirmed damage to both the kidney and the liver. The damage in the liver consisted of necrosis and swollen and vacuolated cells, which appeared to reduce the sinusoidal space. Kidney tubules were atrophied and vacuolated with cell outlines less distinct and cells containing many pyknotic nuclei. Amorphous material was apparent in the lumen of the proximal tubules, and the brush borders were disorganized.

Appenroth et al. (1995) examined the effects of a single i.p. dose of thallium (I) sulfate (5, 10, 15, or 20 mg/kg) on renal function and morphology in adult female Wistar rats. Low doses (i.e., 5 and 10 mg/kg) of thallium (I) sulfate increased the volume of urine (measured on day 2) but did not affect the protein level. Higher doses (i.e., 15 and 20 mg/kg) caused a reduction in urinary volume along with an increase in the urinary protein concentration. The glomerular filtration rate was statistically significantly ($p \leq 0.05$) reduced at 2 days after treatment with 20 mg/kg but had returned to control levels by day 10. Blood urea nitrogen (BUN) levels were significantly ($p \leq 0.05$) increased 2 days after treatment but had returned to normal values by day 10. Histopathology showed a thickening of ascending limb of the loop of Henle notable on day 2 after treatment and resolved by day 10. Na^+/K^+ -ATPase activity was significantly ($p \leq 0.05$) increased in the medulla on day 2 but was significantly ($p \leq 0.05$) reduced by day 5. No changes in Na^+/K^+ -ATPase activity were noted in the cortex.

In follow-up studies, Appenroth et al. (1996) and Fleck and Appenroth (1996) examined the age-related nephrotoxicity of thallium (I) sulfate. Both studies demonstrated that nephrotoxicity was more severe in the adult rat (Wistar) than in young rat (10 or 20 days old) after a single i.p. injection of 20 mg/kg thallium (I) sulfate. Appenroth et al. (1996) determined that there were several biochemical differences in kidney function between 10- and 20-day-old rats (Wistar) administered 20 mg/kg thallium (I) sulfate, but there were no structural changes indicating kidney damage in either group of young rats. In comparison, the thick ascending limb

of loop of Henle in 55-day-old rats showed damage. Thallium did not affect the glomerular filtration rate in either 10- or 20-day-old rats but caused a significant reduction in the rate in 55-day-old rats (Appenroth et al., 1996; Fleck and Appenroth, 1996). Thallium caused a statistically significant ($p < 0.05$) increase in the fractional excretion of a few amino acids (i.e., β -alanine, taurine, and 1-methylhistidine), a statistically significant ($p < 0.05$) decrease in the fractional excretion of glycine in 10-day-old rats, and a statistically significant ($p < 0.05$) increase in the fractional excretion of 13 amino acids in 55-day-old rats. Fleck and Appenroth (1996) determined that thallium affects renal tubular amino acid resorption and causes kidney damage only when mature kidney function is present.

Woods and Fowler (1986) examined the effects of a single i.p. dose of thallium (III) chloride (TlCl_3) at doses of 50, 100, or 200 mg/kg on liver structure and function in male Sprague-Dawley rats (CD strain; 150–200 g) 16 hours after treatment. They determined a dose-related effect on the volume density of mitochondria (increased), rough endoplasmic reticulum (increased), lysosomes (increased), and cytoplasm (decreased). The surface densities of the inner cristae of mitochondria and the rough endoplasmic reticulum also were determined to increase in a dose-dependent manner. Statistically significant ($p < 0.05$) increases occurred in monoamine oxidase (100 and 200 mg/kg) and ferrochelatase (50, 100, and 200 mg/kg). Statistically significant ($p < 0.05$) decreases occurred in aminolevulinic acid (ALA) synthetase (50, 100, and 200 mg/kg), aminopyrrole demethylase (200 mg/kg), aniline hydroxylase (50, 100, and 200 mg/kg), and NADPH cytochrome c (P450) reductase (50, 100, and 200 mg/kg). In addition, *in vitro* studies using 50, 100, or 200 $\mu\text{g/mL}$ TlCl_3 demonstrated a significant ($p < 0.05$) reduction in ALA synthetase, ferrochelatase, aniline hydroxylase, ALA dehydratase, and NADPH cytochrome c (P450) reductase for all dose concentrations. A dose-related loss of ribosomes from the smooth endoplasmic reticulum and proliferation of the rough endoplasmic reticulum were observed through ultrastructural examination. Also observed were generalized mitochondrial swelling and increased numbers of electron-dense autophagic lysosomes.

Table 6 summarizes toxicity data from animal studies involving i.p. or i.v. injection.

Table 6. Thallium toxicity in animals via injection

Reference	Species	Age or weight	Sex	Route/exposure period	Doses	NOAEL/LOAEL	Study type/effect
Acute studies (single dose)							
Ali et al., 1990	Rat	Adult	Male	i.p./single injection	20 mg Tl/kg as thallium (I) acetate	LOAEL=20 mg Tl/kg	Neurological toxicity: neurochemical changes in the brain that were resolved within 24 hrs
Appenroth et al., 1995	Rat	Adult	Female	i.p./single injection	5, 10, 15, and 20 mg/kg thallium (I) sulfate	LOAEL=12 mg Tl/kg	Kidney toxicity: decreased urine volume; increased urine protein; thickened ascending limb of the loop of Henle; changes in brain Na ⁺ /K ⁺ -ATPase
Barroso-Moguel et al., 1990	Rat	Newborn	Both	i.p./single injection	32 mg/kg thallium (I) acetate	LOAEL=25 mg Tl/kg	Neurological toxicity: neuronal and vascular damage in the brain
Barroso-Moguel et al., 1992	Rat	Newborn	Both	i.p./single injection	32 mg/kg thallium (I) acetate	LOAEL=25 mg Tl/kg	Developmental toxicity: diarrhea; alopecia; cartilaginous and osseous tissue alterations; profound skeletal alterations
Barroso-Moguel et al., 1996	Rat	Newborn	Both	i.p./single injection	16 mg/kg thallium (I) acetate	LOAEL=12 mg Tl/kg	Developmental toxicity: diarrhea; muscle atrophy; small size; alopecia; death; interstitial edema between myelin sheaths; thinner muscle fibers; nerve fiber damage
Kuperberg et al., 1998	Rat	250–300 g	Male	i.p./single injection	25 mg/kg thallium (I) acetate	LOAEL=19 mg Tl/kg	Bladder and neurological toxicity: distended bladder; reduced AChE activity in the brain and bladder; increased ChAT activity in the brain and bladder

Table 6. Thallium toxicity in animals via injection

Reference	Species	Age or weight	Sex	Route/exposure period	Doses	NOAEL/LOAEL	Study type/effect
Lameijer and van Zwieten, 1976	Rat	Young adult	Male	i.v./single injection	3-100 mg/kg thallium (I) sulfate	LOAEL=24 mg Tl/kg (30 mg/kg thallium (I) sulfate)	Cardiotoxicity: hypertension
Leung and Ooi, 2000	Rat	210–260 g	Male	i.p./single injection	30, 60, 120 mg/kg thallium (I) sulfate	LOAEL=24 mg Tl/kg	General toxicity: increased AST and ALT; weakness; sluggishness; alopecia; ptosis of the eyelids; diarrhea; respiratory difficulty; liver necrosis; kidney damage
Osorio-Rico et al., 1995	Rat	200–250 g	Male	i.p./single injection	30 or 50 mg/kg thallium (I) acetate	LOAEL=23 mg Tl/kg	Neurological toxicity: increase in MAO and 5-HT in the brain
Woods and Fowler, 1986	Rat	Young adult	Male	i.p./single injection	50, 100, and 200 mg/kg thallium (III) chloride	LOAEL=42 mg Tl/kg	Liver toxicity: increased volume density of mitochondria, lysosomes, and rough endoplasmic reticulum of the liver; decreased cytoplasm in the liver; increased MAO and ferrochelatase; changes in several liver enzymes
Acute studies (3–10 doses)							
Brown et al., 1985	Rat	250 g	Male	i.p./6 days	4 or 8 mg/kg-day thallium (I) acetate	LOAEL=3.1 mg Tl/kg-day	Neurological toxicity: increased lipid peroxidation in the brain; increased β -galactosidase activity in the brain; behavioral changes
Gibson and Becker, 1970	Rat	Fetus; 8, 9, and 10 or 12, 13, and 14 days of gestation	Both	Transplacental via i.p. injection to dam/3 days	2.5 or 10 mg/kg-day thallium (I) sulfate	LOAEL=1.9 mg Tl/kg-day	Developmental toxicity: reduced fetal body weight; increase in hydronephrosis; increase in missing or non-ossified vertebral bodies

Table 6. Thallium toxicity in animals via injection

Reference	Species	Age or weight	Sex	Route/exposure period	Doses	NOAEL/LOAEL	Study type/effect
Gibson and Becker, 1970	Rat	Pregnant	Female	i.p./3 days	2.5 or 10 mg/kg-day thallium (I) sulfate	LOAEL=1.9 mg Tl/kg-day	General toxicity: diarrhea; lethargy; irritability; poor hair luster; alopecia
Hasan et al., 1977	Rat	~150 g	Male	i.p./7 days	5 mg/kg thallium (I) acetate	LOAEL=3.9 mg Tl/kg-day	General toxicity: anorexia; poor hair luster; diarrhea; difficulty walking; abnormal head rotation; lethargy; death; changes in Golgi complexes and smooth cisternae/vesicles of hypothalamic neurons; decreased succinic dehydrogenase and guanine deaminase activities in the brain
Hasan et al., 1978	Rat	~150 g	Male	i.p./7 days	5 mg/kg thallium (I) acetate	LOAEL=3.9 mg Tl/kg-day	Neurological toxicity: decreased dopamine, norepinephrine, and 5-HT in the brain
Hasan and Ali, 1981	Rat	~150 g	Male	i.p./7 days	5 mg/kg thallium (I) acetate	LOAEL=3.9 mg Tl/kg-day	General toxicity: anorexia; poor hair luster; diarrhea; difficulty walking; abnormal head rotation; lethargy; increased lipid peroxidation; aggregation of lipofuscin granules in the perikarya of cerebellar neurons
Hasan and Haider, 1989	Rat	~150 g	Male	i.p./6 days	5 mg/kg thallium (I) acetate	LOAEL=3.9 mg Tl/kg-day	Neurological toxicity: reduced glutathione

Table 6. Thallium toxicity in animals via injection

Reference	Species	Age or weight	Sex	Route/exposure period	Doses	NOAEL/LOAEL	Study type/effect
Kuperberg et al., 1998	Rat	250–300 g	Male	i.p./5 days	0, 0.1, 1.0, or 5.0 mg/kg thallium (I) acetate	LOAEL= 0.08 mg Tl/kg-day	Neurological toxicity: difficulty walking and maintaining pressure on the hind paws; loss of coordination in motor activity; lethargy; reduced food consumption; distended bladder; decreased AchE activity in the bladder
Subchronic study							
Galván-Arzate et al., 2000	Rat	200–250 g	Male	i.p./30 days	0.8 or 1.6 mg/kg-day thallium (I) acetate	LOAEL=0.6 mg Tl/kg-day	Neurological toxicity: increased lipid peroxidation in the brain

4.4.2. Cardiotoxicity

Male Wistar rats (180 to 220 g) injected i.v. with 3 to 100 mg/kg thallium (I) sulfate, while under pentobarbital anesthesia, rapidly developed hypotension with the lowest blood pressures reached within 3 to 5 minutes (Lameijer and van Zwieten, 1976). Blood pressures dropped in a dose-dependent manner with doses of 30 to 100 mg/kg causing a drop of 20 to 40% from initial values and a maximum effect achieved in the 50 to 100 mg/kg range. Thallium had a greater effect on the diastolic pressure. After 10 minutes, animals injected with doses ranging from 3 to 40 mg/kg had blood pressures resembling those prior to thallium injection. The higher doses had a more permanent effect on the blood pressure. In addition to lower blood pressure, the rats had a dose-dependent decrease in heart rate with no maximum achieved. Rats treated with 100 mg/kg had heart rates that were one-third their pre-injection rates. The same effects were observed in anesthetized cats when injected i.v. with monovalent thallium but not when the thallium was infused into the left vertebral artery (Lameijer and van Zwieten, 1976).

4.4.3. Neurotoxicity

No studies of thallium neurotoxicity following exposures by the oral, inhalation or dermal routes of exposure were identified. All studies reported in this section used intraperitoneal (i.p.), subcutaneous (s.c.) or intravenous (i.v.) routes of exposure.

A single i.p. injection of 20 mg/kg thallium (I) acetate in 8–12 (exact number per group not specified) adult male Sprague-Dawley rats (~300 g) resulted in a statistically significant ($p < 0.02$) decrease in aspartate and taurine in the hippocampus 6 hours after treatment that was resolved by 24 hours (Ali et al., 1990). The frontal cortex had a statistically significant ($p < 0.05$) increase in glutamine and taurine at 6 hours. While the glutamine returned to control levels by 24 hours, the taurine was still significantly elevated. A dose-dependent decrease in dopamine and muscarinic cholinergic receptor binding in caudate nucleus was not reported in these treated rats but was observed in caudate nucleus incubated in vitro with thallium. The study report indicated that the effect was not observed 24 hours after the last subacute dose (5 mg/kg daily for 10 days, i.p.) of thallium (I) acetate in a separate study, but the results were not presented. The subacute study demonstrated a statistically significant ($p < 0.05$) increase in dopamine, 3,4-dihydroxyphenylacetic acid, and 5-hydroxytryptamine (5-HT; serotonin) levels in the amygdala nucleus, as well as an increase in 5-HT in the hypothalamus. Dopamine, 3,4-dihydroxyphenylacetic acid, and 5-HT remained similar to control concentrations in the caudate nucleus, frontal cortex, and hippocampus.

A set of companion studies in newborn Wistar rats (Barroso-Moguel et al., 1996, 1990) demonstrated severe and progressive lesions in nerve fibers following i.p. administration of thallium (I) acetate. In the first study (Barroso-Moguel et al., 1990), 32 mg/kg thallium (I)

acetate was given to 15 newborn Wistar rats. Equal numbers were sacrificed at 24, 48, and 72 hours and on days 7 and 51 (3 rats/time point). Alterations in the capillary vessel walls of the brain, observed within the first hours after thallium injection, progressed to irregular thickened walls and fibrotic sclerosis, which obstructed the lumen by 51 days postexposure. Other changes in the brain began in a diffuse manner with all sections affected. Cortical neurons developed the first and most intense lesions; by 51 days, the cortical neurons had mostly disappeared and lesions were apparent in the central grey nuclei.

In a follow-up study (Barroso-Moguel et al., 1996), 16 mg/kg thallium (I) acetate was administered via i.p. injection to 20 newborn Wistar rats (10 each sacrificed at 8 and 50 days of age). General toxicity was manifested through diarrhea, progressive muscular atrophy, small body size, and persistent alopecia. Eight of the 20 thallium-treated rats died during the study. By 8 days of age, thallium-treated rats had interstitial edema between the myelin sheaths (causing separation of the nerve fibers), edema around some axons and within the myelin, and, in some cases, initial damage and degeneration of the myelin sheaths. In addition, muscle fibers were thinner and showed signs of beginning progressive muscular atrophy. Hemorrhage, necrosis, and destruction of the striation were present in some areas of the muscle. By 50 days of age, the rats developed nerve damage with progressive disappearance of nerve fibers and granular, filiform, and amorphous inclusions in abnormal axons and collapsing myelin sheaths. At this time, the muscle fibers lost their transverse striation. Other muscle fibers were observed to be atrophic, fragmented, and exhibiting hyaline degeneration and initial fibroblast reaction; further, some were infiltrated with phagocytic macrophages.

Osorio-Rico et al. (1995) measured monoamine oxidase (MAO) activity and 5-HT turnover rates in different regions of the brain in 127 male Wistar rats (200–250 g) 24 hours after an i.p. administration of 30 or 50 mg/kg aqueous thallium (I) acetate. Results demonstrated MAO was significantly ($p < 0.05$) increased at 30 mg/kg in the midbrain (27.7% over controls) and pons (37% over controls) sections. MAO increases also were observed at 50 mg/kg in the midbrain (48% over controls) and pons (47%). 5-HT turnover was significantly increased in the pons (172% over controls; $p < 0.001$) after 30 mg/kg treatment and in the pons (166.7% over controls; $p < 0.001$) and midbrain (56% over controls; $p < 0.01$) after 50 mg/kg treatment. No significant changes were observed in the dopamine turnover rate.

Subcutaneous injection of thallium (I) acetate as acute (single dose of 20–50 mg/kg), subacute (2–3 weekly injections of 10–15 mg/kg), or chronic (10–20 mg/kg, followed by weekly injections of 5 mg/kg or occasionally 2.5 mg/kg for up to 26 weeks) doses to male and female Sprague-Dawley rats (250–500 g) caused toxicity in all treatment groups (Herman and Bensch, 1967). Symptoms reported in all groups included diarrhea, marked weight loss, anorexia, and lethargy. Animals dosed acutely displayed the symptoms earlier than those on subacute or

chronic dosing schedules. Chronically exposed animals also had hair loss (maximal at 2–4 weeks after initial injection), irritability, and dragging of the hind limbs. Animals were sacrificed when signs of toxicity became apparent.

In acutely exposed animals, the mitochondria of the brain were frequently filled with an overabundance of stacked mitochondrial cristae. Three of four animals administered thallium (I) acetate subacutely had changes in the brain including occasional foci of perivascular cuffing with lymphocytes and hemosiderin-filled macrophage, acute necrosis, and swollen histiocyte-like cells. Peripheral nerves had occasional dense bodies in an unmyelinated nerve plexus. Brain neurons had numerous lipofuscin bodies as did the neurons of the chronically exposed animals.

Twenty-four hours after a single dose of 25 mg/kg thallium (I) acetate, acetyl cholinesterase (AChE) activity was reduced in the hypothalamus and nucleus accumbens (NA) regions of the brain and the activity of choline acetyltransferase (ChAT) activity was significantly ($p \leq 0.05$) increased (Kuperberg et al., 1998). At 48 hours, the AChE in the hypothalamus was still significantly ($p \leq 0.05$) reduced, the AChE in the NA region of the brain was back to control levels. AChE activity also was reduced in the duodenum, and the sphincter-trigon region of the bladder following this single high dose while choline acetyltransferase (ChAT) activity was significantly ($p \leq 0.05$) increased in the ileum, duodenum, and both regions of the bladder. After 48 hours, the AChE levels in the duodenum and the sphincter-trigon and detrusor regions of the bladder were still significantly ($p \leq 0.05$) reduced.

Adult male Sprague-Dawley rats (250–300 g) administered 0.1, 1.0, or 5.0 mg/kg thallium (I) acetate (i.p.) daily for 5 days exhibited difficulty walking and maintaining pressure on their hind paws, loss of coordination in motor activity, lethargy, and reduced food consumption (Kuperberg et al., 1998). Most of the rats (6 of 8) treated at the high dose died by 48 hours post-treatment. The only significant changes observed 24 hours after the last dose were a reduction of AChE levels in the NA region of the brain with the 1.0 mg/kg dose, and an increase in the AChE levels in the striatum and midbrain of rats treated with 5 mg/kg. There was a decrease in AChE activity in the sphincter-trigon region of the bladder at 24 hours in all of the repeat-dose groups (i.e., 0.1, 1.0, and 5.0), which had returned to control values by 48 hours. Decreased bladder AChE levels were also observed in the detrusor region of the bladder 24 hours after 1.0 or 5.0 mg/kg doses and 48 hours after the 0.1 mg/kg dose. The bladders of these rats were distended and contained twice the amount of urine seen in the controls.

Brown et al. (1985) examined lipid peroxidation in the brain after thallium exposure. In this study, groups of male Sprague-Dawley rats (250 g) were administered daily i.p. injections of 4 or 8 mg/kg thallium (I) acetate in water for 6 days. Controls received saline. Twenty-four hours after the final injection behavioral analysis was performed and the following morning, rats were sacrificed. A dose-dependent increase in lipid peroxidation was observed in the

cerebellum, brain stem, and striatum but not in the midbrain and hippocampus. The 8-mg/kg dose also caused a statistically significant ($p < 0.05$) increase in the lipid peroxidation of the cortex. Beta-galactosidase activity followed a dose-dependent increase in the cerebellum, brain stem, and cortex. The 8-mg/kg dose also caused a statistically significant ($p < 0.05$) increase in beta-galactosidase activity in the midbrain and hippocampus. The beta-galactosidase activity in the striatum was not statistically significantly changed by either dose. In general, thallium decreased the frequency of grooming behavior while the frequency of exploratory and attention behaviors was increased. However, the changes were not dose dependent.

Male Charles Foster rats (approximately 150 g) injected with 5 mg/kg thallium (I) acetate daily for 7 days were anorexic, failed to gain weight, had poor hair luster and diarrhea, dragged their hindlimbs, and had fits of abnormal rotation of the head and neck (Hasan and Ali, 1981). All rats were lethargic after 4–5 days of treatment. Rats were sacrificed the day after the final dose (day 8) and their brains were removed and separated into sections. A statistically significant ($p < 0.001$) increase in lipid peroxidation was reported in the cerebral hemisphere, cerebellum, and brain stem by 49, 142, and 116%, respectively. Electron microscopy demonstrated prominent aggregation of lipofuscin granules in the perikarya cerebellar neurons (cell body of neurons in the brain) in thallium-treated rats that were hardly discernible in control rats. Comparisons made with nickel- and cobalt-treated rats demonstrated differences in the areas of increased lipid peroxidation. Nickel and cobalt both had the greatest impact on the brain stem, whereas thallium had a greater effect on the cerebellum. Although Hasan and Ali (1981) could not relate this to the differences in behavioral observations, they did note that nickel- and cobalt-treated rats were irritable and restless; these symptoms were not observed in the thallium-treated rats.

Using a similar protocol to Hasan and Ali (1981), Hasan et al. (1977) administered 5 mg/kg thallium (I) acetate i.p. for 7 days to albino male rats (weighing approximately 150 g). Controls received sodium acetate solution in equal volumes with the same molar concentration. Clinical symptoms were similar to those reported above by Hasan and Ali (1981) with 8/55 treated rats dying by day 7. Electron microscopy showed an increased incidence of well-developed Golgi complexes and curved conformation of smooth cisternae and vesicles of the neurons in the hypothalamus. More significantly, there was a peculiar isolation of axonal endings of the anterior hypothalamus by membranous circumferential lamellae, which appeared to have arisen from the neighboring astrocytic processes. In addition, the succinic dehydrogenase and guanine deaminase activities in the cerebrum were significantly decreased in thallium-treated rats. Protein levels, monoamine oxidase, adenosine triphosphate, and protease levels in the cerebrum were unaffected. Mitochondrial succinic dehydrogenase also was decreased in the cerebrum of thallium-treated rats.

Hasan and colleagues also examined the effects of thallium (I) acetate on neurotransmitter levels and sulfhydryl groups in the brain. Charles Foster rats (approximately 150 g) were administered 5 mg/kg thallium (I) acetate i.p. for 6 (Hasan and Haider, 1989) or 7 (Hasan et al., 1978) days. Dopamine, norepinephrine and 5-HT were reduced in the four sections of the brain examined (hypothalamus and limbic area, corpus striatum, cerebellum, and brain stem), but not all reductions were statistically significant. Dopamine was significantly reduced in the hypothalamus and limbic area (50%; $p < 0.05$) and corpus striatum (64%; $p < 0.01$). Norepinephrine was reduced by 9–33% depending on the brain region, but none of these reductions were statistically significant. 5-HT was significantly reduced in the corpus striatum (53%; $p < 0.001$), cerebellum (36%; $p < 0.05$), and brain stem (66%; $p < 0.001$) (Hasan et al., 1978). Glutathione was significantly ($p < 0.001$) reduced in the cerebrum (56%), cerebellum (62%), and brain stem (74%), and sulfhydryl radicals were significantly ($p < 0.05$) reduced in the cerebellum (25%) and brain stem (32%) (Hasan and Haider, 1989).

Galván-Arzate et al. (2000) administered 0.8 mg/kg (considered 1/40 of the median lethal dose [LD₅₀]) or 1.6 mg/kg (considered 1/20 of the LD₅₀) thallium (I) acetate in deionized water via i.p. injection for 30 days to male Wistar rats (200–250 g). Three days after treatments ended, rats were sacrificed and their brains were dissected into 5 different regions (hypothalamus, cerebellum, frontal cortex, hippocampus, and corpus striatum). In each region, with the exception of the cerebellum, significant ($p < 0.01$) increases in thallium content were observed after administration of 1.6 mg/kg compared to administration of 0.8 mg/kg. There were no statistically significant differences in the deposition of thallium within each region of the brain for each dose. The rate of lipid peroxidation, a marker of oxidative stress, was increased significantly ($p < 0.01$) in the corpus striatum (182%) and cerebellum (130%) after treatment with 0.8 mg/kg. At 1.6 mg/kg, all 5 regions exhibited statistically significant increases in lipid peroxidation over controls (corpus striatum, 161% increase, $p < 0.05$; hippocampus, 114% increase, $p < 0.01$; hypothalamus, 100% increase, $p < 0.01$; cerebellum, 81% increase, $p < 0.01$; and frontal cortex, 80% increase, $p < 0.05$). The two regions affected at 0.8 mg/kg (i.e., corpus striatum and cerebellum) were not affected to a greater extent at the higher dose. Lipid peroxidation was measured to determine if oxidative stress plays a role in thallium's toxicity. The study authors concluded that additional studies need to be performed to establish the precise mechanism of neurotoxicity.

4.5. MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION

Several, possibly related, mechanisms have been postulated for the toxic action of thallium; however, the exact mechanism(s) of toxicity is unknown.

4.5.1. Interference with Potassium Transport

Monovalent thallium is similar to potassium (K^+) in ionic radius and electrical charge, which may contribute to its toxic properties.

Monovalent thallium has been demonstrated to have a 10-fold higher affinity for rabbit kidney Na^+/K^+ -ATPase than does potassium (Britten and Blank, 1968). Barrera and Gómez-Puyou (1975) reported that monovalent thallium also inhibits the influx and efflux of potassium in rat liver mitochondria at concentrations (10 to 15 nmol bound monovalent thallium per mg of mitochondrial protein) that do not affect oxidative phosphorylation. This inhibitory effect of thallium seemed to be specific for potassium since it did not affect the movement of sodium.

Monovalent thallium was completely equilibrated by human red blood cells in 30 minutes in a high (140.5 mM)-sodium (Na^+) medium (Cavieres and Ellory, 1974) but was equilibrated even faster when the medium contained a low concentration (5 mM Na^+). In the high- Na^+ medium containing 1 mM external potassium, monovalent thallium caused a dose-dependent decrease in the ouabain-sensitive potassium influx. Monovalent thallium had a different effect in a medium containing 0.17 mM potassium; low (0.2 mM or less) monovalent thallium ion concentrations stimulated the ouabain-sensitive potassium influx but inhibited it at higher concentrations. Monovalent thallium also had an inhibitory effect on the ouabain-sensitive sodium efflux. It was suggested that the effects on ouabain-sensitive sodium efflux and potassium influx are related to thallium's high-affinity substitution of potassium at the external potassium sites of the sodium pump, which is actively transporting monovalent thallium ions in while pumping sodium ions out.

4.5.2. Disturbance of Mitochondrial Function and Induction of Oxidative Stress

Thallium may exert toxicity by disturbing mitochondrial function. Thallium (I) acetate caused an uncoupling of oxidative phosphorylation and swelling of isolated mitochondria, and induced an increase in oxygen consumption and lactic acid production in ascite tumor cells in vitro (IPCS, 1996).

Other research suggests that thallium may trigger toxicity through induction of oxidative stress. Hanzel et al. (2005) investigated effects of thallium (III) hydroxide on metabolism of glutathione (GSH), which plays a key role in the regulation of cell redox state, in an in vitro system using rat brain cytosolic fractions. Thallium hydroxide decreased the content of reduced glutathione and inhibited glutathione peroxidase and glutathione reductase activity, suggesting that thallium impairs the glutathione-dependent antioxidant defense system. Using rat pheochromocytoma (P12) cells in vitro incubated with both thallium (I) nitrate and thallium (III) nitrate, Hanzel and Verstraeten (2006) found a concentration- and time-dependent decrease in

cell viability, decreased mitochondrial membrane potential, increased steady-state levels of mitochondrial hydrogen peroxide (H_2O_2 , a product of partial reduction of molecular oxygen whose generation is enhanced when electron transport is impaired), and reduced glutathione content. These investigators postulated that both ionic species of thallium enhance reactive oxygen species production in the cell, decreasing mitochondrial functionality and cell viability.

Galvan-Arzate et al. (2005) investigated the effects of a single dose (8 or 16 mg/kg, i.p.) of thallium acetate on lipid peroxidation in different brain regions of Wistar rats (as an indicator of oxidative damage) and alterations in endogenous antioxidant systems. Lipid peroxidation was increased in three of five brain regions at day 7 post-exposure (but not at days 1 and 3) and at the 16 mg/kg; antioxidants GSH and superoxide dismutase (SOD) showed only a modest depletion in only one or two brain regions.

4.5.3. Reaction with Thiol Groups

The capacity of thallium to react with thiol groups, thereby interfering with a variety of processes, is postulated as another mechanism of toxicity, although interference with the metabolism of sulfur-containing amino acids does not seem to be directly involved in toxicity (IPCS, 1996). Thallium (I) chloride formed complexes with a number of sulphur-containing amino acids (i.e., L-cysteine, DL-penicillamine, N-acetyl-L-cysteine, and N-acetyl-DL-penicillamine) in aqueous solution (Bugarin et al., 1989). Because the thallium (I) complexes formed were weaker than those formed using dimethylthallium (III), the study authors concluded that this was unlikely to be the major mechanism of toxicity.

4.5.4. Other Endpoint-specific Mechanistic Data

Cardiotoxicity

Monovalent thallium ions caused a dose-dependent decrease in the heart rate and contractile force of spontaneously beating atria of guinea pigs (Lameijer and van Zwieten, 1976). At a concentration of 10^{-3} M, monovalent thallium reduced the heart rate by approximately 60%. When the isolated atria were electrically driven, monovalent thallium ions at doses up to 10^{-3} M were not able to significantly decrease the amplitude of contraction. Neither potassium (ranging from 0.0024 M to 0.0094 M) nor cocaine (10^{-6} or 10^{-5} M) were able to influence the reduction in heart rate or contractile force of spontaneously beating guinea pig atria caused by monovalent thallium ions (0.0005 M) (Lameijer and van Zwieten, 1976).

Isolated rat heart (from albino rats of both sexes) perfused with a nitrate-Krebs solution containing monovalent thallium ions (as thallium (I) nitrate) in place of potassium had a rapid decrease in beat frequency (Hughes et al., 1978). The heart stopped completely in an average of 7 minutes. Placing the hearts in normal or nitrate-Krebs saline allowed for some recovery in

approximately 10 minutes. The monovalent thallium ions were still present in the heart tissue (9 mmol Tl^+ /kg wet tissue) after 30 minutes in thallium-free solution; this residual thallium caused the heartbeat frequency and amplitude to remain low. When only a portion of the potassium was replaced with monovalent thallium ions, there was a concentration ratio and time dependency on the reduction of the heart rate. In a separate experiment, it was noted that injecting thallium (I) nitrate into the perfusion stream close to the heart caused an initial acceleration of the heartbeat followed by a reduction in amplitude until at certain concentrations the heart stopped. The heartbeat could recover somewhat following nitrate-Krebs perfusion, but the heartbeat frequency and amplitude did not return to initial values and were instead comparable to those values noted prior to the heart stopping. There was a dose-dependent effect on the length of the cardiac paralysis (5–25 μmol monovalent thallium ions injected). The use of potassium nitrate instead of thallium (I) nitrate also caused a dose-dependent increase in the length of cardiac paralysis, but the length of paralysis was shorter than that with thallium (I) nitrate. Further, potassium nitrate-treated hearts recovered completely when washed with nitrate-Krebs solution (Hughes et al., 1978).

Neurotoxicity

Wiegand et al. (1984) recorded the frequencies (reflects presynaptic processes) and amplitudes (reflects postsynaptic processes) of miniature endplate potentials (MEPPs) from neuromuscular junctions of rat (strain not specified) phrenic nerve (of the diaphragm) preparations. Investigators reported a gradual increase in the frequency of MEPPs by a factor of 10 within 30 and 180 minutes at doses of 1×10^{-3} and 5×10^{-4} mol/L thallium (I) acetate, respectively, which was reversible. The amplitude was unchanged. Therefore, it was concluded that thallium interferes presynaptically with spontaneous transmitter release. A follow-up experiment using triangularis sterni muscles of adult mice (strain not specified) demonstrated that although thallium disturbed the presynaptic transmission in a manner similar to divalent metal cations, thallium (monovalent; compound used not specified) acted via a different mechanism than either divalent cobalt or cadmium (Wiegand et al., 1990). This study also demonstrated that thallium did not influence the presynaptic potassium or calcium channels.

Hippocampal slices from adult guinea pigs or rats (strain not specified) were used to examine the effects of thallium on central neuronal activity (Lohmann et al., 1989). The study authors did not note any differences between the guinea pig and rat results and appear to have combined the results. Light microscopy did not show any morphological changes in thallium-treated hippocampal slices even with a high concentration (1–1.2 mM) for 6 hours. Thallium was determined to reversibly reduce the amplitudes of the compound action potential of CA1 pyramidal cells in a dose- and time-related manner. Thallium did not alter intracellular response

parameters, indicating that membrane potential and input resistance were not affected, but postsynaptic potentials were inhibited. The study authors concluded that in the hippocampal slices thallium reacts mainly with postsynaptic target sites and exerts an unknown influence on intracellular metabolism of CA1 pyramidal cells (Lohmann and Wiegand, 1996; Lohmann et al., 1989).

Diaphragms from male and female albino rats perfused with a nitrate-Krebs solution containing monovalent thallium (as thallium (I) nitrate) in place of potassium (K^+) had an initial (1–2 minute) increase in the contraction amplitude, followed by a steady decline in response (Hughes et al., 1978). Four experiments were performed with the sequence taking 20–40 minutes to block indirect (nerve) stimulation and 70–100 minutes to block direct (muscle) stimulation. After returning the diaphragms to normal nitrate-saline, the block in response was reversed, but contraction amplitudes were 30% of the original response for both nerve and muscle after a 75-minute perfusion. The presence of monovalent thallium in the solution, whether as a replacement or an addition to potassium, caused a dose dependency to the response.

Diaz and Monreal (1994) examined the effects of thallium compounds [thallium (III) chloride, thallium (III) nitrate, and thallium (I) acetate] on proton and chloride permeabilities through myelin lipid bilayers using an in vitro system of liposomes prepared with lipids from brain myelin. Trivalent thallium, but not monovalent thallium, mediated a rapid chloride/hydroxyl ion exchange through the lipid bilayers. Trivalent thallium in the presence of reducing agents did not have the same reaction. The ion exchange was faster with trivalent thallium than with mercury (Hg^{+2}). In addition, the reaction occurred with a 10-fold lower concentration of trivalent thallium than of mercury.

Dermal Toxicity

Arbiser et al. (1997) examined the effects of thallium acetate on three types of skin cells, human keratinocytes, primary endothelial cells, and melanoma cells, to determine whether thallium affected cell growth and differentiation in vitro. Inhibition of proliferation of all three cell types was observed. In melanoma cells, thallium caused dose-dependent decreases in cell dendricity and shape, but not cellular motility. In normal human keratinocytes, thallium appeared to interfere with the normal program of cutaneous keratinization. In an in vivo study by the same investigators using piebald LPJ mice with both melanin rich and poor areas in the same animal, one week administration of thallium acetate (5 mg/kg daily) by i.p. injection produced evidence of lipid peroxidation in skin in a perifollicular distribution (Arbiser et al., 1997). [The investigators noted that lipid peroxidation in vivo results in oxidation of lipid membranes, resulting in increased concentrations of aldehydes, which can react with the Schiff reagent thereby producing a colored product.] It was suggested that lipid peroxidation may

result in cell death due to membrane damage, and may partly account for thallium-induced alopecia.

4.5.5. Genotoxicity

Positive results were obtained for thallium (I) nitrate (0.001 M) in the recombination-repair (Rec) assay using *Bacillus subtilis* strains H17 and M45; whether or not hepatic homogenates were used was not specified (Kada et al, 1980; Kanematsu et al., 1980). These positive results were obtained using “cold incubation,” which increases the sensitivity of the assay by 20–50 times for many drugs. In this test, plates containing the bacteria with a 10-mm filter paper disk containing the metal solution (0.05 mL) were incubated at 4°C for 24 hours prior to being incubated at 37°C overnight. The differences in the inhibition of growth between the Rec⁺ strain and the Rec⁻ strain were measured. Thallium (I) nitrate was not mutagenic in reverse mutation assays using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (histidine reversions) and *Escherichia coli* strains B/r WP2 tr⁻ and WP2 her⁻ tr⁻; whether or not hepatic homogenates were used was not specified (Kanematsu et al., 1980). Negative results were obtained in a screening assay for the induction of mitogenic gene conversion and reverse mutation in the yeast, *Saccharomyces cerevisiae*, at a 0.1 M concentration of thallium (I) nitrate (Singh, 1983).

Thallium (I) nitrate did not affect cell division in *S. cerevisiae* (isolated from baker’s yeast) and *E. coli* (strain B) but proved toxic to the aerobic growth processes of *S. cerevisiae* (Loveless et al., 1954). A dose of 250 µg/mL thallium (I) nitrate caused a 50% reduction in aerobic growth processes. The report did not identify specific doses of thallium (I) nitrate tested. The organisms were treated under conditions of logarithmic phase growth. *S. cerevisiae* was incubated for 4 hours with thallium (I) nitrate, and *E. coli* was incubated for 1.5 hours. The study authors noted that several of the other compounds tested (e.g., iodoacetamide) that were specific inhibitors of sulfhydryl groups also reduced the growth processes with no effect on cellular division.

A concentration of 1000 µg/mL thallium (I) acetate reduced viability of Chinese hamster ovary (CHO) cells in culture to 20% with a concomitant decrease in DNA synthesis (i.e., 1% of control values) (Garrett and Lewtas, 1983). The EC₅₀ values (concentration necessary to produce a 50% response) were 307 µg/mL for viability and 18 µg/mL for DNA synthesis. Thallium acetate also depressed ATP and protein synthesis in culture.

Single-strand DNA breaks occurred in cell cultures of C57BL/6 mouse and rat embryo fibroblasts exposed to thallium (I) carbonate at both concentrations tested in mouse fibroblasts (i.e., 10⁻⁵ and 10⁻⁴ M) and all three concentrations tested in rat fibroblasts (i.e., 10⁻⁶, 10⁻⁵, and 10⁻⁴ M) (Zasukhina et al., 1983). However, thallium (I) carbonate did not induce single-strand DNA

breaks in CBA mouse fibroblasts after treatment with 10^{-4} – 10^{-6} M concentrations.

Zasukhina et al. (1983) performed a dominant lethal test on male white rats that received daily oral doses of thallium (I) carbonate (0.005–0.5 $\mu\text{g}/\text{kg}\text{-day}$) for eight months and were subsequently mated with untreated females. Female rats were sacrificed on day 20, and mutagenic potential was evaluated based on evidence of embryotoxicity. The investigators reported an increase in embryonic death, suggestive of a dominant lethal effect. As reported previously (Section 4.3), however, confidence in this study is low. The number of resorptions was highest in the control group. In addition, methods were not adequately reported and results were not analyzed statistically.

4.6. SYNTHESIS OF MAJOR NONCANCER EFFECTS

4.6.1. Oral

Thallium is readily absorbed through the GI tract and distributed throughout the organs and tissues of the body. Although thallium is not metabolized, it occurs in two valence states. If or how the body modifies the valence state of thallium is unknown, but orally administered monovalent thallium and trivalent thallium appear to be distributed in a similar manner throughout the body (Sabbioni et al., 1980a, b). Once thallium is distributed, elimination occurs mainly in the urine and feces with the amounts in each varying by species.

Most of the available human case reports are the results of poisonings, suicide attempts, or accidental ingestion of rodenticides. The lowest known dose to cause symptoms is a single dose of 0.31 g; the patient recovered after treatment (Cavanagh et al., 1974). The only studies of repeated oral exposure to thallium were two surveys of populations exposed to thallium through contaminated homegrown foods (Dolgner et al., 1983; Brockhaus et al., 1981). Limitations in these epidemiology studies included the lack of objective tests for toxicity, reliance on the incidence of symptoms obtained from questionnaires, and characterization of chronic thallium exposure by measuring the levels in urine and hair at a single point in time. Three studies of occupationally exposed populations (Ludolph et al., 1986; Marcus, 1985; Schaller et al., 1980) did not conclusively establish an association between thallium exposure and impaired health status; however, all three studies were limited in terms of size of the study population and study design.

Symptoms of thallium toxicity are diverse in both humans and animals. The triad of gastroenteritis, polyneuropathy, and alopecia has been regarded as the classic syndrome of thallium poisoning (IPCS, 1996), although not all three of these effects are observed in all poisoning cases, and other symptoms develop in varying sequence depending on the magnitude and duration of thallium exposure.

The nervous system as a target organ of thallium is supported by observations from

human case reports and animal studies. Relatively high doses of thallium cause neurological symptoms in humans (e.g., paresthesia of the hands and feet, weakness, tremors, coma, and convulsions). Some of these neurological symptoms (e.g., paresthesia and weakness) were reversible, although recovery was slow. Other effects, including mental and/or psychological problems, were more persistent. Neurological symptoms have also been associated with chronic exposure to thallium in humans. These symptoms include sleep disorders, tiredness, weakness, nervousness, headache, other psychic alterations, and neurological and muscular problems. In experimental animal studies, thallium exposure has been associated with biochemical changes, lipid peroxidation, and histopathological changes in the brain and functional and histopathological changes in peripheral nerves. The areas affected in the brain differ with the age of the treated animal; nevertheless, all measured endpoints (symptoms, biochemical measurements, and histopathology) indicate that high doses (close to lethal doses) of thallium induce significant degradation of the nervous system. Results from in vitro studies further confirm these observations.

Although paresthesia of the hands and feet are trademark symptoms of thallium toxicity, it is generally alopecia that leads to a diagnosis of thallium poisoning in humans. Alopecia occurs about 2 weeks after exposure and is reversible after exposure to thallium is discontinued. Alopecia has also been repeatedly observed in experimental animals exposed to thallium compounds.

Thallium exposure in humans has been associated with respiratory effects and gastrointestinal effects, including diarrhea and vomiting. Other toxic effects associated with oral thallium exposure in humans and animals are changes in blood pressure (high, low, and fluctuating values have all been noted) and liver and kidney damage (kidney damage is age dependent and occurs only in mature kidneys), all of which appear to be reversible with the removal of thallium exposure. Doses that do not affect survival have been shown to affect clinical chemistry parameters such as ALT, AST, BUN, blood glucose, and blood sodium levels, indicating liver and kidney damage with subchronic exposures (Leung and Ooi, 2000; Fleck and Appenroth, 1996; Appenroth et al., 1996, 1995; El-Garawany et al., 1990; Mourelle et al., 1988).

Thallium salts have been shown to affect reproductive function. A dose as low as 0.7 mg Tl/kg-day (10 ppm of thallium (I) sulfate) resulted in testicular damage and reduced sperm motility in male Wistar rats within 60 days (Formigli et al., 1986). Wei (1987) reported that doses as low as 0.001 mg/L in the drinking water for 6 months in Kunming mice reduced sperm motility (rapid speed only), and 0.01 mg/L reduced overall sperm motility and sperm counts and caused a reduction of live offspring while also increasing the number of dead offspring. Confidence in this study is low, however, due to the non-reporting of water consumption and body weights within dose groups.

Limited data in humans and experimental animals suggest that thallium may produce developmental toxicity. A review of case studies of women exposed orally to high levels (approximately 120 to 1100 mg) of thallium during pregnancy suggested a trend toward premature and low-birth-weight infants, especially if exposure took place in the last trimester; no other developmental abnormalities were identified (Hoffman, 2000). Dolgner et al. (1983) examined birth defects in a German population living near a cement plant emitting thallium dusts during the mid-1970s and found a higher incidence of congenital malformations than the incidence documented in the government birth records from the area. The association between the number of birth defects and thallium exposure was weak, however, because two of the malformations were considered hereditary and the incidence for birth defects, although greater than that determined from civil records, was consistent with that reported in the literature. Confidence in this study was limited by lack of exposure data during pregnancy and possible underreporting in controls. In vivo data in rats support an association between intraperitoneal thallium exposure and low birth weight, although such an association has not been reported with orally administered thallium. In vitro data demonstrated an increase in bone malformations in both rat and chick embryos.

4.6.2. Inhalation

There are currently no studies that examine the effects of inhaled thallium. A few case reports (Hirata et al., 1998; Ludolph et al., 1986) suggest an association between occupational exposure and toxicity (including alopecia, gastrointestinal symptoms, and neuropathy), but the route or routes of exposure in these workplace setting could not be established. A study of a population living near a cement factory emitting thallium (Dolgner et al., 1983) determined that thallium exposure occurred via consumption of plants grown in thallium-contaminated soil to a greater extent than via inhalation.

4.6.3. Mode of Action Information

The precise mechanism of thallium toxicity is unknown. Both potassium and thallium are monovalent cations with similar atomic radii (Tl^+ : 1.50 Å, and K^+ : 1.38 Å) (Ibrahim et al., 2006). Thallium has been shown to replace potassium in the reaction of Na^+/K^+ -ATPase (Barrera and Gómez-Puyou, 1975; Britten and Blank, 1968) and to mimic the biological actions of potassium. Monovalent thallium has been shown to have a 10-fold higher affinity than potassium for Na^+/K^+ -ATPase and thus replaces potassium as a substrate for this enzyme (Barrera and Gómez-Puyou, 1975; Britten and Blank, 1968). In other studies it caused a decrease in Na^+/K^+ -ATPase activity in the liver and kidney (Yoshida et al., 1997; Mourelle et al., 1988). After a single oral or intraperitoneal dose of thallium (10 mg/kg orally or 25 mg/kg i.p.),

the disruption of Na⁺/K⁺-ATPase activity was found to be reversible.

Thallium's activity as a Lewis acid with an affinity for organosulfur compounds (Lewis bases) may account for its adverse effect on hair production. Keratin is the primary protein found in hair. It is rich in the amino acid cysteine and its low solubility is, in large part, the product of the formation of inter-polypeptide cysteine-cysteine crosslinks during post-translational modification of the nascent polypeptides. Thallium prevents keratinization of hair proteins by binding with cysteine and preventing the formation of the crosslinking bonds (Mulkey and Oehme, 1993), a property that may be related to the alopecia observed in humans and animals following thallium exposure. Binding to cysteine may also account for inhibition of enzymes with active site cysteine residues and increases oxidative stress as a result of GSH modification (Mulkey and Oehme, 1993).

4.7. EVALUATION OF CARCINOGENICITY

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), there is "inadequate information to assess the carcinogenic potential" for thallium and thallium compounds. There are presently no studies that evaluate the carcinogenic potential of thallium in animals and no adequate studies of humans chronically exposed to thallium.

Two studies of chronic health effects in workers exposed to thallium are available (Marcus, 1985; Schaller et al., 1980), but these studies are inadequate for the assessment of carcinogenicity. The study by Marcus (1985) is limited by the examination of medical records only, lack of exposure quantitation, small cohort size, and the unknown length of observation. Schaller et al. (1980) identified health effects in a worker population at a single time point through medical histories and physical examinations for unspecified symptoms. Worker exposures to thallium were limited to a single measure of urinary thallium, which would not provide an adequate measure of past exposure. This health evaluation was not adequate to detect any carcinogenic response.

Relatively few studies have examined the genotoxicity of thallium compounds; these studies provide inconsistent evidence for genotoxicity. Positive results were obtained at 0.001M for thallium (I) nitrate in the Rec assay using *B. subtilis* strains H17 and M45 (Kanematsu et al., 1980). However, negative results were obtained in reverse mutation assays using several *S. typhimurium* and *E. coli* strains and mitogenic gene conversion and reverse mutation tests in yeast. Cytotoxic levels (1000 µg/mL) of thallium (I) acetate caused depressed DNA synthesis in CHO cells (Garrett and Lewtas, 1983). Single-strand DNA breaks occurred in C57Bl/6 mouse and rat embryo fibroblasts exposed to thallium carbonate but not in similarly exposed CBA mouse fibroblasts (Zasukhina et al., 1983). A dose of 200 mg thallium sulfate caused a slight increase in SCEs in peripheral blood lymphocytes taken from a 48-year-old man on day 1 and

day 15 postexposure and caused a 3.5-fold increase in binucleated cells with micronuclei (Hantson et al., 1997).

4.8. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

There are little or no data available to establish a particular subpopulation as being particularly susceptible to the toxic effects of thallium salts.

4.8.1. Possible Childhood Susceptibility

Exposures in human case reports generally are poorly characterized. Therefore, no comparison can be made between children and adults with regard to susceptibility. In rats, doses of thallium that caused maternal toxicity have been demonstrated to affect the developing fetus (Gibson and Becker, 1970). The only studies that examined the toxic effects of thallium at different ages were those of Appenroth et al. (1996) and Fleck and Appenroth (1996), which focused on the age-related effects on nephrotoxicity. In these studies, mature rats were determined to be more susceptible to kidney damage than young (10 or 20 days old) rats, as mature kidney function appeared necessary for thallium to adversely affect the kidney.

4.8.2. Possible Gender Differences

Leloux et al. (1987), MRI (1988), and Downs et al. (1960) are the only available toxicity studies of thallium compounds using both male and female rats. LeLoux et al. (1987) administered only a single lethal dose of thallium (I) nitrate to rats and thus did not provide findings useful for discerning possible gender differences. Downs et al. (1960) reported slight differences in thallium (III) oxide toxicity between the sexes, with males dying earlier, exhibiting greater and more severe alopecia, and having more profound decreases in body weight than females. No sex-related differences in response were noted in rats treated with thallium (I) acetate (Downs et al., 1996). No marked differences in response were noted in male and female rats after exposure to thallium (I) sulfate (MRI, 1988); however high-dose female rats exhibited a higher incidence of alopecia than males, and hair follicle atrophy was observed in females only. Overall, the limited data do not identify any consistent pattern of gender-related differences in response to thallium exposure.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

5.1.1. Choice of Principal Study and Critical Effect—with Rationale and Justification

As discussed in Section 4.6.1., most information on thallium toxicity in humans comes from poisonings, suicide attempts, or accidental exposures, and epidemiological studies of the general population or occupationally-exposed populations are limited in terms of study design and insufficient exposure characterization. Thus, available human study findings do not provide data useful for dose-response analysis.

There are only three repeat-dose oral studies of thallium compound toxicity that used more than one dose level: Downs et al. (1960), Wei (1987), and MRI (1988). Other repeat-dose studies of thallium oral toxicity used study designs not appropriate for dose-response analysis, including single-dose only studies (El-Garawany et al., 1990; Rossi et al., 1988; Formigli et al., 1986; Gregotti et al., 1985; Manzo et al., 1983) or studies that suffered from critical reporting deficiencies (Zasukhina et al., 1983; see Section 4.3). In the Downs et al. (1960) study of thallium (I) acetate, mortality in two control groups was 30-40%, complicating interpretation of the findings in treated rats (mortality and alopecia). A study of thallium (III) oxide by the same investigators (Downs et al., 1960) failed to identify a NOAEL. Further, death in 2 of 5 female rats at the lowest dose tested in this study was observed and may have been treatment related. Wei (1987) reported effects on sperm count, motility, and viability in Kunming mice exposed to relatively low concentrations of thallium (I) carbonate in drinking water; however, the reproductive index and number of implantations in the dosed mice were not affected by treatment. Doses associated with drinking water levels were not reported by the study authors, and water consumption and terminal body weight data for the mice from which dose estimates could be derived were not provided by the study authors. Further, the mouse strain used in this study was a nonstandard strain. For these reasons, the study data in Wei (1987) were considered to be of low confidence and not appropriate for dose-response analysis. The subchronic (90-day) toxicity study of thallium (I) sulfate in Sprague-Dawley rats (MRI, 1988) is the most comprehensive study of thallium toxicity and was conducted according to EPA GLPs. This study examined sensitive measures of thallium toxicity and identified the lowest NOAEL among subchronic toxicity studies. Accordingly, this study was selected as the principal study for derivation of the RfD.

In the MRI (1988) study, rats (20/sex/group) were treated by gavage daily for 90 consecutive days with 0, 0.01, 0.05, or 0.25 mg/kg-day of an aqueous solution of thallium (I) sulfate (approximately 0, 0.008, 0.04, or 0.20 mg Tl/kg-day). There were no differences observed among control groups and groups receiving thallium sulfate for body weight, body

weight gains, food consumption, or absolute and relative organ weights. In male rats, the incidence of alopecia was increased over the controls, although the increase was not dose related (i.e., 10, 5, 20, 45, and 20% for the untreated control, vehicle control, 0.008, 0.04, and 0.2 mg Tl/kg-day, respectively). In females, a dose-related increase in the incidence of alopecia was observed (i.e., 20, 5, 20, 45, and 60% for the untreated control, vehicle control, 0.008, 0.04, and 0.2 mg Tl/kg-day, respectively). The study authors related the occurrence of alopecia to cyclic patterns of hair growth and concluded that the results were not biologically significant. The study authors also characterized some of the cases of alopecia as “not totally attributed to barbering behavior.” The incidence of cases of alopecia in females not totally attributed to barbering behavior showed a dose-related increase (0, 0, 5, 15, 25% for the untreated control, vehicle control, 0.008, 0.04, and 0.2 mg Tl/kg-day, respectively). The study authors identified the highest dose (0.20 mg Tl/kg-day) as a NOAEL based upon a lack of biological significance for the observed effects (alopecia in females).

At the high dose, however, histologic examination of skin samples from two high-dose females showed atrophy of hair follicles. These two animals also exhibited alopecia. Hair loss (alopecia) is characteristic of thallium poisoning in humans and experimental animals (Ibrahim et al., 2006; Galván-Arzate and Santamaría, 1998), and typically occurs in humans within two weeks of exposure. It is hypothesized that thallium’s affinity for sulfhydryl groups may be responsible for alopecia; thallium prevents keratinization of hair proteins by binding with cysteine. Skin biopsies have been taken from a limited number of patients with alopecia and other symptoms of thallium poisoning; these biopsies have revealed atrophic and necrotic changes of the skin (Lu et al., 2007; Heyl and Barlow, 1989; Saddique and Peterson, 1983). For example, skin biopsy findings from two patients who ingested water that contained thallium included parakeratosis, dilated hair follicles filled with keratin and necrotic sebaceous materials, mild epidermal atrophy, and vacuolar degeneration of the basal layer (Lu et al., 2007).

In summary, female rats exhibited a dose-related increase in alopecia, an effect characteristic of thallium toxicity. Although alopecia was observed in controls as well as thallium-exposed rats, females exhibited a dose-related increase in alopecia that was statistically significantly elevated over controls at the mid- and high-doses, and also exhibited a dose-related increase in the incidence of alopecia that could not be totally attributed to barbering behavior (see Table 4). The finding of two cases of atrophy of the hair follicles in high-dose female rats with alopecia is consistent with the atrophic changes observed in cases of human thallium poisoning, and provides additional support that alopecia at the high-dose (0.2 mg Tl/kg-day) is likely related to thallium exposure. Whether alopecia is itself an adverse effect merits consideration. In humans, alopecia is generally reversible upon cessation of thallium exposure. Alopecia, however, appears to be a part of a continuum of dermal changes observed following

thallium exposure, as well as one of a spectrum of effects on target organs that include the nervous and gastrointestinal systems. For these reasons, alopecia supported by two cases of hair follicle atrophy is considered adverse. Accordingly, the high dose, 0.25 mg/kg-day thallium (I) sulfate, is considered to be the LOAEL, and the mid dose, 0.05 mg/kg-day thallium (I) sulfate, the NOAEL. The equivalent NOAEL and LOAEL for thallium only are 0.04 and 0.2 mg TI/kg-day, respectively.

Review of the LOAELs from studies of subchronic exposure duration (see Table 5) shows the LOAEL of 0.2 mg TI/kg-day from MRI (1988) to be generally consistent with the LOAELs from other experimental animal studies (0.7 to 1.8 mg TI/kg-day). A comparison of LOAELs across subchronic studies suggests that the nature of response to thallium (I) salts may sharply increase in severity with increasing dose. For example, treatment-related mortality (15-21%), as well as alopecia and nerve histopathology, were observed following a 36-week exposure to 1.4 mg TI/kg-day (Manzo et al., 1983), a dose only sevenfold higher than the LOAEL of 0.2 mg TI/kg-day for alopecia alone from MRI (1988). By way of comparison, the lowest exposure associated with acute thallium-related toxicity in humans is approximately 4 mg/kg (Cavanagh et al., 1974)² – a dose 20-fold higher than the repeat-dose LOAEL from MRI (1988), and exposures reported to be lethal to humans are as low as 6 mg/kg (IPCS, 1996) – a dose 30-fold higher than the LOAEL from MRI (1988).

5.1.2. Methods of Analysis

The NOAEL-LOAEL approach was used to derive an RfD for thallium salts. A benchmark dose (BMD) analysis was not conducted because the incidence of histopathologically-determined hair follicle atrophy was not considered amenable to BMD methods. There were only two groups to consider, with histopathological examination of the skin performed for high-dose and vehicle control groups only. Two of 20 female rats in the high-dose group (10%) had hair follicle atrophy and alopecia that was consistent with thallium toxicity in both animals and humans and was thus characterized as treatment-related. The majority of cases of alopecia in the control and dosed groups was attributed to barbering behavior or normal cyclic hair growth patterns. Given the background occurrence of alopecia in study animals and the potential for misclassification, there is some uncertainty about the incidence of possibly treatment-related alopecia in treated animals.

Thus, the NOAEL of 0.04 mg TI/kg-day from MRI (1988) was used as the point of departure for developing the RfD.

² Based on a toxic dose of 0.31 g/person and assuming a body weight of 70 kg.

5.1.3. RfD Derivation—Including Application of Uncertainty Factors (UFs)

Soluble Thallium Salts: Acetate, Carbonate, Chloride, Nitrate, and Sulfate

The principal study used to derive the RfD (MRI, 1988) involved administration of thallium (I) sulfate. There are no studies of thallium (I) acetate, thallium (I) carbonate, thallium (I) chloride, or thallium (I) nitrate that are appropriate as the basis for an RfD. For the following reasons, it was considered appropriate to treat these monovalent thallium salts as toxicologically equivalent to thallium (I) sulfate when expressed in terms of thallium. It is likely that the mechanism of toxicity is the same for these salts due to the fact that they all contain monovalent thallium ions and are water soluble. There are only small differences in the toxicity of various water-soluble thallium (I) salts in mice, rats, rabbits, and dogs. In general, for most laboratory species at an observation period of approximately 1-2 weeks, the LD₅₀ or minimum effective dose (MED) values range between 10 and 30 mg/kg body weight for thallium (I) salts, independent of the exposure route (IPCS, 1996). Therefore the use of thallium (I) sulfate as a surrogate for the other thallium salts is appropriate.

The RfD for thallium is derived using the NOAEL of 0.04 mg Tl/kg-day and applying a total uncertainty factor of 3000 (10 for interspecies extrapolation, 10 for intraspecies extrapolation, 3 for extrapolation from a subchronic to chronic study, and 10 for database deficiencies).

- A default interspecies uncertainty factor of 10 was applied for extrapolation from laboratory animals to humans. No information was available to characterize the toxicokinetic or toxicodynamic differences between experimental animals and humans.
- A default intraspecies uncertainty factor of 10 was applied to account for variation in human susceptibility in the absence of information on the variability of response to thallium in the human population.
- Because no chronic toxicity studies for thallium are available, an uncertainty factor of 3 was applied to account for extrapolation from subchronic to chronic exposure duration. Oral toxicity data for thallium suggests that a full default uncertainty factor of 10 would overestimate the difference in response following subchronic and chronic oral exposures. Alopecia, the critical effect used to derive the RfD, occurs within weeks of exposure to thallium (i.e., this sensitive effect does not require chronic exposure in order to manifest), and once hair loss has occurred, the effect cannot

change in nature or severity. Thus, for this particular endpoint, the uncertainty associated with use of a subchronic study can reasonably be characterized as smaller than the default factor of 10.

- An uncertainty factor for LOAEL to NOAEL extrapolation was not needed because the principal study identified a NOAEL.
- The thallium database includes several subchronic oral toxicity studies in rats. Studies of reproductive and developmental toxicity of thallium compounds in rats and mice are available; however, these studies used nontraditional study designs that did not provide adequate testing of reproductive or developmental endpoints. In reproductive toxicity studies by Gregotti et al. (1985) and Formigli et al. (1986), male rats only were exposed for periods up to 60 days and evaluation of reproductive toxicity was limited to examination of male reproductive organs. In two other reproductive toxicity studies, male rats (Zasukhina et al., 1983) or mice (Wei, 1987) only were exposed to thallium compounds for 6 to 8 months and mated with untreated females. Confidence in these latter two studies was low (see Section 4.3). No studies of reproductive toxicity in exposed females and no multigeneration reproductive toxicity study were identified. Developmental toxicity by the oral route was limited to Rossi et al. (1988) in which rats were exposed to thallium sulfate from gestation day 1 through 60 days of age or from birth through 60 days of age. No investigation of developmental endpoints at the end of the gestation period was performed. Despite the limitations in the available reproductive and developmental toxicity studies, the available studies provide suggestive evidence that thallium compounds can adversely affect male reproductive organs and the developing fetus and highlight the deficiencies in the current thallium database. Limited neuropathological examinations were included in the subchronic toxicity studies by MRI (1988) and Manzo et al. (1993), but no neurobehavioral studies were identified. Because the nervous system is a sensitive target of thallium toxicity, the limited investigation of thallium neurotoxicity represents a data deficiency. Thus, a database uncertainty factor of 10 was applied to account for a lack of adequate developmental toxicity studies and a two-generation reproductive toxicity study, and additional uncertainty associated with the limited data available on neurotoxicity in light of the potential for neurotoxicity to represent a sensitive endpoint for thallium exposure.

Thus, the RfD for thallium (I) is calculated as:

$$0.04 \text{ mg Tl/kg-day} \div 3000 = 1 \times 10^{-5} \text{ mg Tl/kg-day}$$

RfD values for individual soluble thallium salts can be derived using the formula weight ratio of the thallium salt to the thallium in the salt (molecular weight = 204) as follows:

- $0.04 \text{ mg Tl/kg-day} \times (\text{molecular weight of the soluble salt} \div \text{molecular weight of thallium in the salt}) = \text{converted NOAEL for the specific thallium salt}$
- For example, the NOAEL for thallium (I) acetate (molecular weight = 263) is estimated as $0.04 \text{ mg Tl/kg-day} \times 263/204 = 0.05 \text{ mg/kg-day}$

RfDs for soluble thallium salts based on the NOAEL for a given thallium salt and a total uncertainty factor of 3000 are listed in Table 7.

Table 7. Reference doses for soluble thallium salts

Soluble thallium salt	Molecular weight	Converted NOAEL	RfD
Thallium (I) acetate TlC ₂ H ₃ O ₂	263	0.05 mg/kg-day	2×10^{-5} mg/kg-day
Thallium (I) carbonate Tl ₂ CO ₃	469	0.05 mg/kg-day	2×10^{-5} mg/kg-day
Thallium (I) chloride TlCl	240	0.05 mg/kg-day	2×10^{-5} mg/kg-day
Thallium (I) nitrate TlNO ₃	266	0.05 mg/kg-day	2×10^{-5} mg/kg-day
Thallium (I) sulfate Tl ₂ SO ₄	505	0.05 mg/kg-day	2×10^{-5} mg/kg-day

Insoluble Thallium Salts: Thallium (III) Oxide

There are no oral studies of thallium (III) oxide that are adequate to support derivation of an RfD. Downs et al. (1960) administered thallium (III) oxide to Wistar-derived albino rats via the diet for 15 weeks at exposure concentrations of 0, 20, 35, 50, 100, and 500 ppm. The study reported only body weights, mortality, kidney weights, and limited histopathology. Because all relevant endpoints were not evaluated, treatment group sizes were small (five per group per sex), and few animals survived to termination, this study could not be used to derive an RfD.

Because of differences in the physical-chemical properties of thallium (I) sulfate and

thallium (III) oxide, thallium (I) sulfate is not considered to be an appropriate surrogate. Unlike thallium (I) sulfate, thallium (III) oxide is insoluble in water. Thallium (I) sulfate contains monovalent thallium (Tl^{+1}), while thallium (III) oxide contains trivalent thallium (Tl^{+3}). Although the gastric environment may increase the solubility of thallium (III) oxide, no studies are available that examine the effects of the gastric pH and gastric environment on the valence state of thallium (III) oxide.

Limited evidence from the toxicology literature suggests that distribution of thallium (I) and thallium (III) compounds and lethality of these two compounds may be comparable. Sabbioni et al. (1980a) determined that, following oral administration of either inorganic monovalent thallium (Tl^{+1}) as thallium (I) sulfate or trivalent thallium (Tl^{+3}) as thallium (III) chloride, there was a similar distribution of thallium in the tissues (valence state could not be determined) at 16 hours and 8 days after administration, indicating that the valence state of thallium did not affect tissue distribution (and presumably uptake). Downs et al. (1960) demonstrated similar oral 7-day LD_{50} values for thallium (I) acetate (32 mg Tl/kg) and thallium (III) oxide (39 mg Tl/kg) in female rats, indicating that lethality may be independent of valence state. However, other endpoints could respond differently to different valence states of thallium. Monovalent thallium compounds have been determined to behave similarly to potassium (K^{+}), thus disrupting $Na^{+}-K^{+}$ -ATPase and the systems dependent on this transporter (e.g., liver and kidney). Trivalent thallium has not been demonstrated to behave in the same manner. A single in vitro study of mono- and trivalent thallium compounds (Diaz and Monreal, 1994) suggested that biological responses to thallium in the (I) and (III) valence states may differ. Using an in vitro system with liposomes prepared with lipid from brain myelin, these investigators reported that trivalent thallium, but not monovalent thallium, mediated a rapid chloride/hydroxyl ion exchange through the lipid bilayers.

Given the lack of conclusive evidence that the valence state of thallium changes following uptake, toxicity attributable to monovalent thallium may not apply to trivalent thallium.

Thallium (I) Selenite

No toxicity studies of thallium selenite are available. Thallium (I) selenite contains monovalent thallium as does thallium (I) sulfate. There is no information in the literature, however, on the water solubility of thallium selenite. In the absence of solubility information, it cannot be determined if thallium sulfate is an appropriate surrogate for thallium selenite. Accordingly, the available data do not support derivation of an RfD for thallium selenite.

5.1.4. Previous RfD Assessment

The previous IRIS RfD values for thallium (I) acetate, thallium (I) carbonate, thallium (I) chloride, thallium (I) nitrate, and thallium (I) sulfate were posted to the IRIS database in September 1988. These assessments were based on the same principal study by Midwest Research Institute (MRI) as the current assessment. [The principal study was previously cited as U.S. EPA (1986c). MRI subsequently issued a revised final report in 1988, which is the basis for the current RfD. There are no substantive differences in the findings and conclusions between the 1986 and 1988 versions of MRI report.] Previous RfD values (adjusted for differences in molecular weight) ranged from 8×10^{-5} to 9×10^{-5} mg/kg-day. These RfD values were based on a NOAEL of 0.25 mg/kg-day thallium sulfate, the highest dose tested by MRI (1988), and application of a composite uncertainty factor of 3000 (10 to extrapolate from subchronic to chronic data, 10 for intraspecies extrapolation, 10 to account for interspecies variability, and 3 to account for lack of reproductive and chronic toxicity data). Although the same principal study is used (MRI, 1988), the current oral RfD value for soluble thallium salts (acetate, carbonate, chloride, nitrate, and sulfide) is based on a NOAEL of 0.05 mg/kg-day thallium sulfate. The difference in the NOAEL between the 1988 and current assessment reflects an alternative interpretation of the MRI (1988) findings (i.e., that the finding of two cases of alopecia in high-dose [0.05 mg/kg-day thallium sulfate] female rats with atrophy of the hair follicles is an adverse health effect and results in an RfD 4 to 4.5-fold lower than the RfDs posted to IRIS in 1988. The total UF applied in the 1988 and current assessment is the same (i.e., 3000), although the component UFs are different. The current assessment includes a UF for subchronic to chronic extrapolation of 3 and a UF for incomplete database of 10, whereas the 1988 assessment applied a UF of 10 for subchronic to chronic extrapolation and 3 for incomplete database. A reduction of the subchronic to chronic UF from 10 to 3 reflects the revised interpretation of the alopecia findings and the conclusion that application of a full default uncertainty factor of 10 would overestimate the difference in response following subchronic and chronic oral exposures. Alopecia is an effect that occurs within weeks of exposure to thallium (i.e., does not require chronic exposure in order to manifest), and once manifested, does not change in nature or severity. An increase in the database UF from 3 to 10 reflects a reconsideration of the uncertainties associated with the current database (i.e., a lack of adequate developmental toxicity studies and a two-generation reproductive toxicity study, and additional uncertainty associated with the limited data available on neurotoxicity in light of the potential for neurotoxicity to represent a sensitive endpoint for thallium exposure). See Section 5.1.3 for additional justifications for the UFs used in the current assessment.

The RfD values for thallium (I) selenite and thallium (III) oxide were withdrawn in 1993 and 1989, respectively. The absence of an RfD for these two thallium compounds in the current assessment is in agreement with the previous IRIS file.

5.1.5. Uncertainties in the Oral Reference Dose (RfD)

Risk assessments need to describe associated uncertainty. The following discussion identifies uncertainties associated with the RfD for thallium and compounds. As presented earlier in this section (5.1.2 and 5.1.3), the uncertainty factor approach (U.S. EPA, 2002, 1994b, 1993) was used to derive the RfD for thallium. Using this approach, the point of departure (POD) was divided by a set of factors to account for uncertainties in the RfD related to the extrapolation from responses observed in animal bioassays to humans and from data from subchronic exposure to chronic exposure, a diverse human population of varying susceptibilities, and database deficiencies. Because of the limited chemical-specific information for thallium to inform the various assumptions and extrapolations, default uncertainty factors were applied.

The available animal and human toxicity literature demonstrates that thallium adversely affects a broad range of target organs (see Section 4), including the nervous, respiratory, gastrointestinal, and reproductive systems, skin, liver, kidney, and possibly the developing organism. Nevertheless, critical deficiencies in the thallium database have been identified; uncertainties associated with these data deficiencies are discussed more fully below.

Selection of the critical effect for reference value determination. Alopecia (hair loss) in rats (as identified in the 90-day MRI [1988] study) was identified as the critical effect for RfD derivation. Numerous studies conducted in animals have documented alopecia as a sensitive outcome of thallium exposure. Alopecia is also the best-known effect of thallium poisoning in humans (Ibrahim et al., 2006; Galván-Arzate and Santamaría, 1998). Hair loss usually occurs within two weeks of exposure and is reversible after exposure to thallium is discontinued. Population surveys and occupational epidemiological investigations do not provide similar evidence for alopecia in thallium-exposed populations; however, it is not clear that any study other than Brockhaus et al. (1981) specifically looked for hair loss in the study population. In a survey of a population living near a cement plant in Lengerich, Germany, Brockhaus et al. (1981) reported a negative correlation between thallium exposure (measured in urine or hair) and hair loss, a finding inconsistent with the observation of alopecia consistently seen in reports of poisonings.

Overall, the many observations of alopecia in animal studies and reports of human poisonings lead to a relatively high degree of certainty that the selected critical effect is relevant to human health assessment, although it is noted that alopecia has not been documented in

population surveys or occupational epidemiological investigations at lower exposures.

Dose-response modeling. The RfD was derived using a NOAEL for the POD. A POD based on a NOAEL or LOAEL is, in part, a reflection of the particular doses (and dose spacing) selected in the principal study. The NOAEL or LOAEL lacks characterization of the dose-response curve and for this reason is less informative than a POD obtained from benchmark dose modeling.

Uncertainty is associated with the identification of the NOAEL from the MRI (1988) study. The study investigators identified the highest dose (0.20 mg Tl/kg-day) as a NOAEL based upon their interpretation of the observed effects (alopecia in females) as not biologically significant. The U.S. EPA, however, interpreted the increasing trend of alopecia and the finding of two cases of atrophy of the hair follicles in female rats to be consistent with evidence of thallium-related toxicity (see Section 5.1.1). Accordingly, the U.S. EPA considered the high dose (0.20 mg Tl/kg-day) to be the LOAEL, and the middle dose (0.04 mg Tl/kg-day) to be the NOAEL. The difference in interpretation of the toxicological significance of alopecia in female rats introduces uncertainty in the selection of the POD. The fact that male rats did not exhibit a similar dose-related increase in alopecia introduces additional uncertainty. U.S. EPA's interpretation of the study findings results in a POD fivefold lower than that of the study investigators.

Animal to human extrapolation. Extrapolating dose-response data from animals to humans is another source of uncertainty. The effect and the magnitude of the effect at the POD in rodents is extrapolated to human response. Uncertainty in interspecies extrapolation can be separated into two general areas—toxicokinetic and toxicodynamic. In the absence of information to quantitatively assess either toxicokinetic or toxicodynamic differences between animals and humans, a 10-fold UF was used to account for uncertainty in extrapolating from laboratory animals to humans in the derivation of the RfD. Thallium-specific data to examine the potential magnitude of over- or under-estimation of this UF is unavailable.

A PBPK model, which could reduce uncertainty in the pharmacokinetic portion of interspecies extrapolation, is not available for thallium.

Intrahuman variability. Heterogeneity among humans is another source of uncertainty. In the absence of thallium-specific data on human variation in response to thallium toxicity, a default uncertainty factor of 10 was used to account for this area of uncertainty in the derivation of the RfD. Human variation may be larger or smaller; however, thallium-specific data to examine the potential magnitude of over- or under-estimation is unavailable.

Subchronic to chronic exposure extrapolation. Because no chronic toxicity studies for thallium are available, a UF of 3 was applied to extrapolate those data obtained from a study of subchronic exposure to chronic exposure. Oral toxicity data for thallium suggests that a full default uncertainty factor of 10 would overestimate the difference in response following subchronic and chronic oral exposures. Alopecia occurs within weeks of exposure to thallium (i.e., this sensitive effect does not require chronic exposure in order to manifest), and once hair loss has occurred, the effect cannot change in nature or severity. Thus, for this particular endpoint, the uncertainty associated with use of a subchronic study can reasonably be characterized as smaller than the default factor of 10.

Data gaps. To the extent that the database for thallium is incomplete, it is possible that certain endpoints of toxicity or certain sensitive lifestages have not been evaluated that could result in PODs lower than those for which study data are available. The thallium database lacks a chronic toxicity study and two-generation reproduction study. Several studies of reproductive and developmental toxicity of thallium compounds in rats and mice are available; however, these studies used nontraditional study designs that provided an incomplete evaluation of reproductive and developmental toxicity endpoints, and in the case of two reproductive toxicity studies, low confidence was assigned to the study findings. Of the available subchronic toxicity studies, only the 90-day MRI (1988) study provided data adequate for dose-response analysis. Deficiencies in the database related to neurotoxicity were also identified. A default uncertainty factor of 10 was used to account for uncertainty associated with deficiencies in the thallium database. Thallium-specific data to examine the potential magnitude of over- or under-estimation is unavailable.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

Information on the inhalation toxicity of thallium is insufficient to derive an inhalation RfC. No studies of inhaled thallium in experimental animals were identified and occupational epidemiology studies involving possible inhalation exposures to thallium were limited and inconclusive.

5.3. CANCER ASSESSMENT

There are no human or animal studies available that are adequate to assess the carcinogenic potential of thallium salts.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

Thallium is well absorbed from the gastrointestinal tract, skin, and respiratory tract and is distributed throughout the body. Thallium, as an element, is not metabolized, but the extent to which it may be converted from one valence state to another (i.e., Tl^{+1} and Tl^{+3}) in the body is not known. Excretion of thallium occurs mainly through the urine and feces, but the amounts are species dependent. Humans mainly excrete thallium through the urine, but it also has been detected in the hair, sweat, tears, and breast milk.

Thallium salts cause a wide spectrum of adverse effects in humans and animals. Alopecia is an effect that is characteristic of thallium exposure. Alopecia generally occurs within 2 weeks of exposure and is reversible when thallium exposure is removed. Only one epidemiological study reported a negative correlation between thallium exposure and hair loss (Brockhaus, 1981); however, this study lacked measures of chronic exposure to thallium and was limited by reliance on questionnaires to determine symptomology in thallium-exposed individuals.

Some study observations suggest that the nervous system may be the primary target organ for thallium salt toxicity which has been observed after a single dose of 0.31 g thallium acetate in an adult male or 1 mg/kg thallium (I) nitrate for 4 days in adult rats. A variety of neurological effects have been reported in humans, including lethargy, back pain, paresthesia of the hands and feet, weakness (including facial weakness), inability to walk, and prolonged mental defects. Some of the effects are reversible depending on the severity, while others are irreversible and may require long-term care. Animal studies support these findings in humans.

Kidney damage in humans has been noted by increases in BUN levels and serum creatinine and is reversible with treatment and/or discontinued exposure to thallium. Data from animal studies support those in humans with regard to kidney damage; thallium-related effects include increased or decreased urine output (depending on dose), protein in the urine, and changes in electrolyte balance. Histopathological examination of thallium-exposed animals revealed changes in kidney morphology, including atrophied and vacuolated kidney tubules, amorphous material in the lumen of the proximal tubules, disorganized brush borders, and thickening ascending limb of the loop of Henle. Na^{+}/K^{+} -ATPase activity in the medulla also was significantly reduced. None of these changes were dose related and were generally seen with large doses of thallium. Animal studies also suggest that kidney toxicity requires mature kidney function. The subchronic (90-day) toxicity study in rats used to derive the RfD showed moderate

increases in AST and LDH, which are general indicators of tissue damage (MRI, 1988). However, a specific relation to possible kidney damage was not indicated due to the lack of changes in other clinical chemistry parameters (i.e., BUN and creatinine) and histopathological changes in the kidney.

Cardiotoxicity findings in thallium-exposed humans are variable. Many case reports indicate hypertension, while a few reported hypotension. Animal studies indicate that thallium affects heart rate and causes a decrease in blood pressure, which also can be related to kidney effects and is supported by in vitro results.

Many of the case reports in humans reported increased ALT and/or AST levels, indicating liver toxicity. These effects returned to normal after patients received medical care for thallium exposure. Various indicators of liver damage, including increases in ALT, AST, serum bilirubin, lipid peroxidation, triglycerides, and serum alkaline phosphatase and decreases in glycogen, glutathione, and liver Na⁺/K⁺-ATPase, have been reported in animal studies. In addition, histopathology revealed swollen and vacuolated cells and swollen mitochondria. Many of these effects were reversible in animals after a single dose of thallium. Statistically significant increases in AST and LDH were observed in the MRI (1988) subchronic (90-day) toxicity study in rats but were not associated with liver damage due to the lack of changes in other clinical chemistry parameters (i.e., ALT) and histopathological changes in the liver.

Low birth weight is a likely adverse effect of thallium exposure in females (humans and animals) exposed during pregnancy. Male mice exposed to thallium had low sperm counts, low sperm motility, and increases in the number of deformed sperm. Testicular effects observed in animals included disarrangement of the tubular epithelium, cytoplasmic vacuolation and distention of smooth endoplasmic reticulum of the Sertoli cells, and reduced beta-glucuronidase activities. Mating exposed male mice to unexposed female mice appeared to cause a decrease in the number of live fetuses and an increase in the overall rate of dead fetuses; however, critical information concerning the doses of thallium administered makes it difficult to assess these results.

There are no human studies relating thallium exposure to developmental toxicity. A literature review of pregnant women exposed to thallium during various stages of pregnancy only related low birth weight with thallium exposure. A survey of children born near a cement plant emitting thallium reported an increase in congenital malformations over those reported to the government; however, the study authors did not consider these malformations to be attributable to thallium exposure because two of the cases were considered hereditary and the incidence was similar to that reported in the literature. Because of various study limitations, the findings are considered inconclusive. In rats exposed transplacentally and/or via mother's milk, then via the drinking water until 60 days of age, thallium (1 mg/dL in the drinking water of dams

then offspring) affected bone development and vasomotor reactivity. Chick embryos exposed to thallium developed achondroplasia; these data further support the potential role of thallium in the disruption of bone development.

There are no studies available to determine the carcinogenic potential of thallium in animals and no adequately conducted studies in humans. The limited number of studies of the genotoxicity of thallium compounds provides inconsistent evidence of genotoxic potential. Under EPA's guidelines for carcinogen risk assessment (U.S. EPA, 2005a), the Agency concluded that there is "inadequate information to assess the carcinogenic potential."

6.2. DOSE RESPONSE

The 90-day gavage toxicity study of thallium (I) sulfate in Sprague-Dawley rats (MRI, 1988) was selected as the principal study. Alopecia was observed in all dose groups, including the control, although the incidence increased in a dose-related pattern. Most, but not all, cases were attributed to barbering behavior in the rats. Histopathological examination revealed atrophy of the hair follicles in 2/20 high-dose female rats (0.25 mg/kg-day thallium sulfate or 0.20 mg Tl/kg-day) that also had alopecia. Because numerous animal studies and human case studies have reported alopecia as an effect of thallium poisoning, the occurrence of alopecia with hair follicle atrophy in high-dose females was considered to be toxicologically significant and the high dose was identified as a LOAEL. The middle dose, 0.05 mg/kg-day thallium (I) sulfate (0.04 mg Tl/kg-day), was considered a NOAEL. Other studies and endpoints were considered in the selection of the critical effect. As shown in Table 5, alopecia was a particularly sensitive endpoint of toxicity. Further, only three other datasets from subchronic studies of thallium compounds included multiple doses that were amenable to dose-response analysis (Downs et al., 1960; Wei, 1987). In the Downs et al. (1960) study of thallium (I) acetate, mortality in two control groups was 30-40%, complicating interpretation of the findings in treated rats (mortality and alopecia). A study of thallium (III) oxide by the same investigators (Downs et al., 1960) failed to identify a NOAEL. Wei (1987) reported effects on sperm count, motility, and viability in mice exposed to relatively low concentrations of thallium (I) carbonate in drinking water; however, study data were not amenable to dose-response quantification.

The NOAEL of 0.04 mg Tl/kg-day from MRI (1988) was used as the POD to derive the RfD. A POD based on a NOAEL or LOAEL is, in part, a reflection of the particular doses (and dose spacing) selected in the principal study. The NOAEL or LOAEL lacks characterization of the dose-response curve and is thus less informative than a POD obtained from benchmark dose modeling. A total uncertainty factor of 3000 (10 for interspecies extrapolation, 10 for intraspecies extrapolation, 3 for extrapolation from a subchronic to chronic study, and 10 for database deficiencies) was applied to the NOAEL to yield an RfD of 1×10^{-5} mg/kg-day for

thallium sulfate. An RfD of 2×10^{-5} mg/kg-day for individual soluble thallium (I) salts (specifically, the acetate, carbonate, chloride, nitrate, and sulfate), based on molar adjustment of the NOAEL for thallium (I) sulfate to account for the different molecular weights of the different thallium salts, was also presented. Information was unavailable to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans and the potential variability in human susceptibility to thallium toxicity; thus, default interspecies and intraspecies UFs of 10 were applied. A UF of 3 was applied to address the uncertainty associated with extrapolation of data obtained from a study of subchronic exposure to chronic exposure. A default database UF of 10 was applied to account for deficiencies in the thallium toxicity database, including lack of a two-generation reproductive toxicity study and studies of cardiotoxicity, neurotoxicity, and immunotoxicity.

Confidence in the RfD for soluble thallium salts is low. Confidence in the principal study, MRI (1988), is medium. This study was conducted in accordance with GLPs, and included examination of sensitive measures of thallium toxicity, including dermal and neurologic endpoints. Group sizes (20 animals/sex) were not particularly large and histopathological examination of the skin was not conducted for all dose groups. Confidence in the identification of the point of departure for the RfD based on MRI (1988) is low. A confidence ranking of low for the point of departure reflects differences in the interpretation of the biological significance of high-dose findings by EPA and the study investigators (and thus the designation of the NOAEL and LOAEL from this study), the occurrence of hair follicle atrophy in female rats only, and the background incidence of alopecia in control animals. Confidence in the database is low to medium. The database includes numerous case reports of thallium poisonings, and several limited studies of environmentally-exposed populations and worker populations. The reports of human poisonings, in particular, provide considerable information on the target organs of thallium in humans. Chronic studies of thallium toxicity in experimental animals have not been performed, and of the thallium salts, only thallium (I) sulfate has been tested in an adequate subchronic toxicity study. Developmental toxicity was investigated in two studies in rats, and male reproductive toxicity in three studies, including a dominant lethal study. One of these reproductive toxicity studies (Wei, 1987) provides evidence that male reproductive toxicity may occur at relatively low drinking water concentrations; however, insufficient reporting precluded dose-response analysis of the findings. Considering the confidence in the principal study, the point of departure, and the database, the overall confidence in the RfD is low.

The available data are not adequate to derive an RfD for thallium (III) oxide or thallium (I) selenite. Inhalation toxicity studies are not available to support derivation of RfCs for any thallium compounds.

7. REFERENCES

- Ali, SF; Jairaj, K; Newport, GD; et al. (1990) Thallium intoxication produces neurochemical alterations in rat brain. *Neurotoxicology* 11:381-390.
- Andre, T; Ullberg, S; Winqvist, G. (1960) The accumulation and retention of thallium in tissues of the mouse. *Acta Pharmacol Toxicol* 16:229-234. (As cited in CEPA, 1999)
- Appenroth, D; Gambaryan, S; Winnefeld, K; et al. (1995) Functional and morphological aspects of thallium-induced nephrotoxicity in rats. *Toxicology* 96(3):203-215.
- Appenroth, D; Tiller, S; Gambaryan, S; et al. (1996) Ontogenetic aspects of thallium-induced nephrotoxicity in rats. *J Appl Toxicol* 16(3):235-243.
- Aoyama, H. (1989) Distribution and excretion of thallium after oral and intraperitoneal administration of thallos malonate and thallos sulfate in hamsters. *Bull Environ Contam Toxicol* 42:456-463.
- Arbiser, JL; Alani, R; Flynn, E; et al. (1997) Effects of thallium ion on cellular components of the skin. *J Dermatol* 24:147-155.
- ATSDR (Agency for Toxic Substance and Disease Registry). (1992) Toxicological profile for thallium. Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available from: <<http://www.atsdr.cdc.gov/toxprofiles/tp54.html>>.
- Atsmon, J; Taliansky, E; Landau, M; et al. (2000) Thallium poisoning in Israel. *Am J Med Sci* 320(5):327-330.
- Barclay, RK; Peacock, WC; Karnofsky, DA. (1953) Distribution and excretion of radioactive thallium in the chick embryo, rat, and man. *J Pharmacol Exp Ther* 107:178-187. (As cited in CEPA, 1999)
- Barrera, H; Gómez-Puyou, A. (1975) Characteristics of the movement of K^+ across the mitochondrial membrane and the inhibitory action of Tl^+ . *J Biol Chem* 250(14):5370-5374.
- Barroso-Moguel, R; Ríos-Castañeda, C; Villeda-Hernández, J; et al. (1990) Neurotoxicity of thallium biochemical and morphological study of organic lesions. *Arch Invest Med* 21:115-122.
- Barroso-Moguel, R; Villeda-Hernández, J; Méndez-Armenta, M; et al. (1992) Osteochondric lesions in developing rats intoxicated with thallium twenty-four hours after birth. *Arch Med Res* 23(3):129-133.
- Barroso-Moguel, R; Méndez-Armenta, M; Villeda-Hernández, J; et al. (1996) Experimental neuromyopathy induced by thallium in rats. *J Appl Toxicol* 16(5):385-389.
- Britten, JS; Blank, M. (1968) Thallium activation of (Na^+-K^+) -activated ATPase of rabbit kidney. *Biochim Biophys Acta* 159:160-166.
- Brockhaus, A; Dolgner, R; Ewers, U; et al. (1981) Intake and health effects of thallium among a population living in the vicinity of a cement plant emitting thallium containing dust. *Int Arch Occup Environ Health* 48:375-389.
- Brown, DR; Callahan, BG; Cleaves, MA; et al. (1985) Thallium-induced changes in behavioral patterns: correlation with altered lipid peroxidation and lysosomal enzyme activity in brain regions of male rats. *Toxicol Ind Health* 1(1):81-98.
- Bugarin, MG; Casa, JS; Sordo, J; et al. (1989) Thallium (I) interactions in biological fluids: a potentiometric investigation of thallium (I) complex equilibria with some sulphur-containing amino acids. *J Inorg Biochem* 35:95-

CEPA (California Environmental Protection Agency) (1999) Public health goal for thallium in drinking water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. Careaga-Olivares, J; Gonzalez-Ramirez, D. (1995) Penicillamine produces changes in the acute blood elimination and tissue accumulation of thallium. *Arch Med Res* 26(4):427-430.

Cavanagh, JB; Fuller, NH; Johnson, HRM; et al. (1974) The effects of thallium salts, with particular reference to the nervous system changes. *Q J Med* 43:293-319.

Cavieres, JD; Ellory, JC. (1974) Thallium and the sodium pump in human red cells. *J Physiol* 243:243-266.

Davis, LE; Standefer, JC; Kornfeld, M; et al. (1981) Acute thallium poisoning: toxicological and morphological studies of the nervous system. *Ann Neurol* 10:38-44.

Diaz, RS; Monreal, J. (1994) Thallium mediates a rapid chloride/hydroxyl ion exchange through myelin lipid bilayers. *Mol Pharmacol* 46:1210-1216.

Dolgnier, R; Brockhaus, A; Ewers, U; et al. (1983) Repeated surveillance of exposure to thallium in a population living in the vicinity of a cement plant emitting dust containing thallium. *Int Arch Occup Environ Health* 52:79-94.

Downs, WL; Scott, JK; Steadman, LT; et al. (1960) Acute and sub-acute toxicity studies of thallium compounds. *Industr Hygiene J* 21:399-406.

Elsenhans, B; Schumann, K; Forth, W. (1991) Toxic metals: interactions with essential metals. In: Rowland, IR; ed. *Nutrition, toxicity, and cancer*. Boca Raton: CRC Press, Inc.; pp. 223-258.

El-Garawany, AA; Samaan, HA; Sadek, M. (1990) Comparative hepatorenal toxicity of some commonly used chemical environmental pollutants. *Egypt J Pharm Sci* 31(1-4):331-336.

Feldman, J; Levisohn, DR. (1993) Acute alopecia: clue to thallium toxicity. *Pediatr Dermatol* 10(1):29-31.

Fleck, C; Appenroth, D. (1996) Renal amino acid transport in immature and adult rats during thallium-induced nephrotoxicity. *Toxicology* 106:229-236.

Formigli, L; Scelsi, R; Poggi, P; et al. (1986) Thallium-induced testicular toxicity in the rat. *Environ Res* 40:531-539.

Forth, W; Rummel, W. (1975) Gastrointestinal absorption of heavy metals. In: Forth, W; Rummel, W; Aguiar, AJ; eds. *International encyclopedia of pharmacology and therapeutics: Section 39B. Pharmacology of intestinal absorption: gastrointestinal absorption of drugs*. Vol. II. Oxford, New York: Pergamon Press; p. 647.

Galván-Arzate, S; Rios, C. (1994) Thallium distribution in organs and brain regions of developing rats. *Toxicology* 90:63-69.

Galván-Arzate, S; Santamaría, A. (1998) Thallium toxicity. *Toxicol. Lett* 99:1-13.

Galván-Arzate, S; Martínez, A; Medina, E; et al. (2000) Subchronic administration of sublethal doses of thallium to rats: effects on distribution and lipid peroxidation in brain regions. *Toxicol Lett* 116:37-43.

Galvan-Arzate, S; Pedraza-Chaverri, J; Medina-Campos, ON; et al. (2005) Delayed effects of thallium in the rat brain: Regional changes in lipid peroxidation and behavioral markers, but moderate alterations in antioxidants, after a single administration. *Food Chem Toxicol* 43:1037-1045.

Garrett, NE; Lewtas, J. (1983) Cellular toxicity in Chinese hamster ovary cell cultures. I. Analysis of cytotoxicity endpoints for twenty-nine priority pollutants. *Environ Res* 32:455-465.

- Gefel, A; Liron, M; Hirsch, W. (1970) Chronic thallium poisoning. *Israel J Med Sci* 6:380-382.
- Gibson, JE; Becker, BA. (1970) Placental transfer, embryotoxicity, and teratogenicity of thallium sulfate in normal and potassium-deficient rats. *Toxicol Appl Pharmacol* 16:120-132.
- Gosselin, RE; Smith, RP; Hodge, HC. (1984) *Clinical toxicology of commercial products*. 5th edition. Baltimore, MD: Williams and Wilkins; pp. III-379 to III-383. (As cited in CEPA, 1999)
- Gregotti, C; Di Nucci, A; Formigli, L; et al. (1985) Altered testicular enzyme patterns in rats after long-term exposure to thallium sulphate. *J Toxicol Clin Exp* 5(4):265-271.
- Gregotti, C; Di Nucci, A; Costa, LG; et al. (1992) Effects of thallium on primary cultures of testicular cells. *J Toxicol Environ Health* 36:59-69.
- Hall, BK. (1972) Thallium-induced achondroplasia in the embryonic chick. *Dev Biol* 28:47-60.
- Hall, BK. (1985) Critical periods during development as assessed by thallium-induced inhibition of growth of embryonic chick tibiae in vitro. *Teratology* 31:353-361.
- Hantson, P; Desoir, R; Leonard, ED; et al. (1997) Cytogenetic observations following thallium poisoning. *J Toxicol Environ Health* 50:97-100.
- Hanzel, CE; Verstraeten, SV. (2006) Thallium induces hydrogen peroxide generation by impairing mitochondrial function. *Toxicol Appl Pharmacol* 216:485-492.
- Hanzel, CE; Villarverde, MS; Verstraeten, SV. (2005) Glutathione metabolism is impaired in vitro by thallium(III) hydroxide. *Toxicol* 207:501-510.
- Hasan, M; Ali, SF. (1981) Effects of thallium, nickel and cobalt administration on the lipid peroxidation in different regions of the rat brain. *Toxicol Appl Pharmacol* 57:8-13.
- Hasan, M; Haider, SS. (1989) Acetyl-homocysteine thiolactone protects against some neurotoxic effects of thallium. *Neurotoxicology* 10:257-262.
- Hasan, M; Chandra, SV; Bajpai, VK; et al. (1977) Electron microscopic effects of thallium poisoning on the rat hypothalamus and hippocampus: Biochemical changes in the cerebrum. *Brain Res Bull* 2:255-261.
- Hasan, M; Ali, SF; Tariq, M. (1978) Levels of dopamine, norepinephrine and 5-hydroxytryptamine in different regions of the rat brain in thallium toxicosis. *Acta Pharmacol Et Toxicol* 43:169-173.
- Herman, MM; Bensch, KG. (1967) Light and electron microscopic studies of acute and chronic thallium intoxication in rats. *Toxicol Appl Pharmacol* 10:199-222.
- Heyl, T; Barlow, RJ. (1989) Thallium poisoning: a dermatological perspective. *Br J Dermatol* 121:787-91.
- Hirata, M; Taoda, M; Ono-Ogasawara, M; et al. (1998) A probable case of chronic occupational thallium poisoning in a glass factory. *Ind Health* 36:300-303.
- Hoffman, RS. (2000) Thallium poisoning during pregnancy: a case report and comprehensive literature review. *Clin Toxicol* 38(7):767-775.
- Hughes, MN; Man, WK; Whaler, BC. (1978) The toxicity of thallium (I) to cardiac and skeletal muscle. *Chem Biol Interact* 23:85-97.
- Ibrahim, D; Frobert, B; Wolf, A; et al. (2006) Heavy metal poisoning: clinical presentations and pathophysiology.

Clin Lab Med 26:67-97.

IPCS (International Programme on Chemical Safety). (1996) Thallium. Environmental health criteria. Vol. 182. World Health Organization, Geneva, Switzerland. Available from: <http://www.inchem.org/documents/ehc/ehc/ehc182.htm>.

Kada, T; Hirano, K; Shirasu, Y. (1980) Screening of environmental chemical mutagens by the Rec-assay system with *Bacillus subtilis*. In: deSerres, FJ; Hollaender, A; eds. Chemical mutagens: principles and methods for their detection; pp. 149-173.

Kanematsu, N; Hara, M; Kada, T. (1980) REC assay and mutagenicity studies on metal compounds. *Mutat Res* 77:109-116.

Karnofsky, DA; Ridgway, LP; Patterson, PA. (1950) Production of achondroplasia in the chick embryo with thallium. *Proc Soc Exp Biol Med* 73:255-259.

Kuo, HC; Huang, CC; Tsai, YT; et al. (2005) Acute painful neuropathy in thallium poisoning. *Neurology* 65:302-4.

Kuperberg, JM; Ngong, JM; Rutledge, LP; et al. (1998) Central and peripheral alteration of the cholinergic enzymes activities of the rat in response to repeated and acute thallium exposure. *Toxic Subs Mech* 17:285-298.

Lameijer, W; van Zwieten, PA. (1976) Acute cardiovascular toxicity of thallium (I) ions. *Arch Toxicol* 35:49-61.

Lameijer, W; van Zwieten, PA. (1977) Kinetic behavior of thallium in the rat: accelerated elimination of thallium owing to treatment with potent diuretic agents. *Arch Toxicol* 37:265-273.

Lehmann, FPA; Favari, L. (1985) Acute thallium intoxication: kinetic study of the relative efficacy of several antidotal treatments in rats. *Archives of Toxicology* 57:56-60. (As cited in CEPA, 1999)

Leloux, M-S; Lich, NP; Claude, J-R. (1987) Experimental studies on thallium toxicity in rats. I. Localization and elimination of thallium after oral acute and sub-acute intoxication. *J Toxicol Clin Exp* 7(4):247-257.

Léonard, A; Gerber, GB. (1997) Mutagenicity, carcinogenicity and teratogenicity of thallium compounds. *Mutation Research* 387:47-53.

Leopold, G; Furukawa, E; Forth, W; et al. (1968) Vergleichende Untersuchungen der Resorption von Schwermetallen in vivo and in vitro. *Naunyn Schmiedebergs Arch Pharmacol* 263:275. (As cited in Elsenhans et al., 1991)

Leung, KM; Ooi, VEC. (2000) Studies on thallium toxicity, its tissue distribution and histopathological effects in rats. *Chemosphere* 41:155-159.

Lie, R; Thomas, RG; Scott, JK. (1960) The distribution and excretion of thallium-204 in the rat, with suggested MPCs and a bio-assay procedure. *Health Phys* 2:334-340. (As cited in U.S. EPA, 1991b)

Limos, CL; Ohnishi, A; Suzuki, N; et al. (1982) Axonal degeneration and focal muscle fiber necrosis in human thallotoxicosis: histopathological studies of nerve and muscle. *Muscle Nerve* 5:598-706.

Lohmann, H; Wiegand, H. (1996) Reduced probability of orthodromically evoked action potential firing in CA1 pyramidal cells of guinea pig hippocampal slices after acute thallium exposure. *Arch Toxicol* 70:430-439.

Lohmann, H; Csicsaky, M; Wiegand, H. (1989) The action of thallium on the excitability of CA1 pyramidal cells in hippocampal slices. *Neurotoxicol Teratol* 11:545-549.

Loveless, LE; Spoerl, E; Weisman, TH. (1954) A survey of effects of chemicals on division and growth of yeast and *Escherichia coli*. *J Bacteriol* 68:637-644.

- Lu, CI; Huang, CC; Chang, YC; et al. (2007) Short-term thallium intoxication. *Arch Dermatol* 143:93-98.
- Ludolph, A; Elger, CE; Sennhenn, R; et al. (1986) Chronic thallium exposure in cement plant workers: Clinical and electrophysiological data. *Trace Elem Med* 3:121-125.
- Lund, A (1956) Distribution of thallium in the organism and its elimination. *Acta Pharmacol Et Toxicol* 12:251-259.
- Manzo, L; Scelsi, R; Moglia, A; et al. (1983) Long-term toxicity of thallium in the rat. In: Brow, SS; Savoy, J; eds. *Chemical toxicology and clinical chemistry of metals*. London: London Academy Press; pp. 401-405.
- Marcus, RL. (1985) Investigation of a working population exposed to thallium. *J Soc Occup Med* 35:4-9.
- Mourelle, M; Favari, L; Amezcua, JL. (1988) Protection against thallium hepatotoxicity by silymarin. *J Appl Toxicol* 8(5):351-354.
- MRI (Midwest Research Institute). (1988) Toxicity of thallium(I) sulfate (CAS No. 7446-18-6) in Sprague-Dawley rats. Volume two: Subchronic (90-day) study. Revised final report. Project No. 8702-L(18), Work Assignment No. 111148-008. Prepared for U.S. Environmental Protection Agency, Office of Solid Waste, Washington, DC, through Dynamac Corporation, Rockville, MD. [An external peer review was conducted by EPA in November 2006 to evaluate the accuracy of experimental procedures, results, and interpretation and discussion of the findings presented. A report of this peer review is available through the EPA's IRIS Hotline, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (e-mail address) and at www.epa.gov/iris.]
- Mulkey, JP; Oehme, FW. (1993) A review of thallium toxicity. *Vet Human Toxicol* 35(5):445-454.
- Munch, JC. (1934) Human thallotoxicosis. *J Am Med Assoc* 102:1929-1934. (As cited in U.S. EPA, 1992)
- Navas-Acien, A; Silbergeld, EK; Sharrett, AR; et al. (2005) Metals in urine and peripheral arterial disease. *Environ Health Persp* 113:164-69.
- NLM (National Library of Medicine). (1998) Thallium. HSDB (Hazardous Substances Data Bank). National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, MD. Available from: <http://toxnet.nlm.nih.gov>.
- NRC (National Research Council). (1983) Risk assessment in the federal government: managing the process. Washington, DC: National Academy Press.
- Osorio-Rico, L; Galván-Arzate, S; Ríos, C. (1995) Thallium increases monoamine oxidase activity and serotonin turnover rate in rat brain regions. *Neurotoxicol Teratol* 17(1):1-5.
- Pearson, RG. (1963) Hard and soft acids and bases. *J Amer Chem Soc* 85:3533-3539.
- Reed, D; Crawley, J; Faro, SN; et al. (1963) Thallotoxicosis. *JAMA* 183(7):516-522.
- Rios, C; Galván-Arzate, S; Tapia, R. (1989) Brain regional thallium distribution in rats acutely intoxicated with Tl_2SO_4 . *Arch Toxicol* 63:34-37.
- Roby, DS; Fein, AM; Bennet, RH; et al. (1984) Cardiopulmonary effects of acute thallium poisoning. *Chest* 85:236-240.
- Rossi, F; Marrazzo, R; Berrino, L; et al. (1988) Prenatal and postnatal thallium exposure in rats: Effect on development of vasomotor reactivity in pups. *Teratog Carcinog Mutagen* 8:13-23.
- Rusyniak, DE; Furbee, RB; Kirk, MA. (2002) Thallium and arsenic poisoning in a small Midwestern town. *Ann Emerg Med* 39(3):307-11.

Sabbioni, E; Goetz, L; Marafante, E. (1980a) Metabolic fate of different inorganic and organic species of thallium in the rat. *Sci Total Environ* 15:123-135.

Sabbioni, E; Marafante, E; Rade, J; et al. (1980b) Metabolic patterns of low and toxic doses of thallium in the rat. *Dev Toxicol Environ Sci* 8:559-564.

Saddique, A ; Peterson, CD. (1983) Thallium poisoning : a review. *Vet Hum Toxicol* 25:16-22.

Saha, A; Sadhu, HG; Karnik, AB; et al. (2004) Erosion of nails following thallium poisoning: a case report. *Occup Environ Med* 61:640-42.

Schaller, KH; Manke, G; Raithel, HJ; et al. (1980) Investigation of thallium-exposed workers in cement factories. *Int Arch Occup Environ Health* 47:223-231.

Schoer, J. (1984) Thallium. In: Hutzinger, O; ed. *The handbook of environmental chemistry*. Vol. 3. Anthropogenic compounds. Part C. Berlin: Springer-Verlag; pp. 143-214. (As cited in CEPA, 1999)

Schwartzman, RM; Kirschbaum, JO. (1961) The cutaneous histopathology of thallium poisoning. *J Invest Dermatol* 39:169-173.

Sharma, AN; Nelson, LS; Hoffman, RS. (2004) Cerebrospinal fluid analysis in fatal thallium poisoning: evidence for delayed distribution into the central nervous system. *Am J Forensic Med Pathol* 25:156-58.

Shaw, PA. (1933) Toxicity and deposition of thallium in certain game birds. *J Pharmacol Exp Ther* 48:478-487. (As cited in U.S. EPA, 1991b)

Singh, I. (1983) Induction of reverse mutation and mitotic gene conversion by some metal compounds in *Saccharomyces cerevisiae*. *Mutat Res* 117:149-152.

Talas, A; Wellhöner, HH. (1983) Dose-dependency of Tl kinetics as studied in rabbits. *Arch Toxicol* 53:9-16.

Talas, A; Pretschner, DP; Wellhöner, HH. (1983) Pharmacokinetic parameters for thallium (I) ions in man. *Arch Toxicol* 53:1-7.

Thomas, ML; McKeever, PJ. (1993) Chronic thallium toxicosis in a dog. *J Am Anim Hosp Assoc* 29:2111-215.

Tsai, Y-T; Huang, C-C; Kuo, H-C; et al. (2006) Central nervous system effects in acute thallium poisoning. *NeuroToxicol* 27:291-295.

U.S. EPA (Environmental Protection Agency). (1986a) Guidelines for the health risk assessment of chemical mixtures. *Federal Register* 51(185):34014-34025.

U.S. EPA (1986b) Guidelines for mutagenicity risk assessment. *Federal Register* 51(185):34006-34012.

U.S. EPA (1986c) Subchronic (90-day) toxicity of thallium sulfate in Sprague-Dawley rats. Office of Solid Waste, Washington, DC.

U.S. EPA (1988) Recommendations for and documentation of biological values for use in risk assessment. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC; EPA 600/6-87/008. Available from: National Technical Information Service, Springfield, VA; PB88-179874/AS.

U.S. EPA (1991a) Guidelines for developmental toxicity risk assessment. *Federal Register* 56(234):63798-63826.

U.S. EPA (1991b) Drinking water health advisory for thallium. Office of Water, Washington, DC. Available from:

National Technical Information Service, Springfield, VA; PB92-135524.

U.S. EPA. (1993) Reference dose (RfD): description and use in health risk assessments. Background Document 1A. March 15, 1993. Available at: <<http://epa.gov/iris/rfd.htm>>.

U.S. EPA (1994a) Interim policy for particle size and limit concentration issues in inhalation toxicity: notice of availability. Federal Register 59(206):53799.

U.S. EPA. (1994b) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, Washington, DC; EPA/600/8-90/066F. Available from: National Technical Information Service, Springfield, VA; PB20000-5000023, and <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA. (1995) Use of the benchmark dose approach in health risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-94/007. Available from: National Technical Information Service, Springfield, VA; PB95-213765, and <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA (1996) Guidelines for reproductive toxicity risk assessment. Federal Register 61(212):56274-56322.

U.S. EPA (1998a) Guidelines for neurotoxicity risk assessment. Federal Register 63(93):26926-26954.

U.S. EPA (1998b) Science policy council handbook: peer review. Office of Science Policy, Office of Research and Development, Washington, DC; EPA 100-B-98-001. Available from: National Technical Information Service, Springfield, VA; PB98-140726, and <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA (2000a) Science policy council handbook: peer review. 2nd edition. Office of Science Policy, Office of Research and Development, Washington, DC; EPA 100-B-00-001. Available from: <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA (2000b) Science policy council handbook: risk characterization. Office of Science Policy, Office of Research and Development, Washington, DC. EPA 100-B-00-002. Available from: <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA (2000c) Benchmark dose technical guidance document [external review draft]. Office of Research and Development, Risk Assessment Forum, Washington, DC; EPA/630/R-00/001. Available from: <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA (2000d) Supplementary guidance for conducting health risk assessment of chemical mixtures. Risk Assessment Forum, Washington, DC; EPA/630/R-00/002. Available from: <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA. (2002) A review of the reference dose and reference concentration processes. Risk Assessment Forum, Washington, DC; EPA/630/P-02/002F. Available from: <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA. (2005a) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from: <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA. (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available from: <<http://www.epa.gov/iris/backgr-d.htm>>.

U.S. EPA. (2006) Science policy council handbook: peer review. 3rd edition. Office of Science Policy, Office of Research and Development, Washington, DC. Available from: <http://www.epa.gov/ncea/iris/Peer_Review_Handbook_2006_3rd_edition.pdf>

Waters, CB; Hawkins, EC; Knapp, DW. (1992) Acute thallium toxicosis in a dog. JAMA 201(6):883-885.

Wei, Q. (1987) Studies on spermotoxicity of thallium carbonate in drinking water and its effect on reproductive

function of mice. *Zhonghua Yu Fang Yi Xue Za Zhi* 21(3):141-143.

Wiegand, H; Papadopoulos, R; Csicsaky, M; et al. (1984) The action of thallium acetate on spontaneous transmitter release in the rat neuromuscular junction. *Arch Toxicol* 55:253-257.

Wiegand, H; Uhlig, S; Gotzsch, U; et al. (1990) The action of cobalt, cadmium and thallium on presynaptic currents in mouse motor nerve endings. *Neurotoxicol Teratol* 12:313-318.

Woods, JS; Fowler, BA. (1986) Alteration of hepatocellular structure and function by thallium chloride: Ultrastructural, morphometric, and biochemical studies. *Toxicol Appl Pharmacol* 83:218-229.

Yokoyama, K; Araki, S; Abe, H. (1990) Distribution of nerve conduction velocities in acute thallium poisoning. *Muscle Nerve* 13:117-120.

Yoshida, M; Igeta, S; Kawashima, R; et al. (1997) Changes in adenosine triphosphate (ATP) concentration and its activity in murine tissues after thallium administration. *Bull Environ Contam Toxicol* 59(2):268-273.

Zasukhina, GD; Vasilyeva, IM; Sdirkova, NI; et al. (1983) Mutagenic effect of thallium and mercury salts on rodent cells with different repair activities. *Mutat Res* 124(2):163-173.

APPENDIX A
Summary of External Peer Review and Public Comments and Disposition